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The Journal of Allergy

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The Journal of Allergy

VOL. III NOVEMBER, 1931 No. 1

Original Articles

THE POLLEN ALLERGEN*

J. H. BLACK, M.D.
DALLAS, TEXAS

SINCE the suggestion of Meltzer[1] that asthma in man bears a striking resemblance to the anaphylactic reaction in the guinea pig, it has been assumed by many workers that asthma is an anaphylactic phenomenon. Others, because of certain immunologic, or clinical, differences from the classical anaphylactic reaction, have insisted upon a separation and the designation of asthma, and allied conditions, as hypersensitiveness, allergy, or atopy.

Regardless of how one may designate these conditions the fact remains that the terms used indicate some type of reaction to an antigen. Because of their apparent relationship and evidence that their fundamental mechanism is identical, all those conditions which we, of this group, commonly designate as allergic, are considered to be dependent upon the same type of reaction to antigen. Since the antigenic activity has been believed to reside in and to be limited to protein substances, it has been generally assumed that allergic conditions are the result of the reaction of the protein constituent of the excitant with the sensitive organism.

Certain difficulties arise in the interpretation of certain reactions on this basis. It is well known, for example, that reactions, indistinguishable by any known means from true allergic reactions, may result from exposure to substances entirely free of nitrogenous constituents. Some workers have evaded this difficulty by assigning these reactions to a separate class, basing this separation on the finding that other allergic conditions usually are accompanied by the presence of an antibody in the circulating blood of the sensitive person, while in those reacting to nonnitrogenous excitants, antibody usually is not found. Zinsser[2] believes that this difference might be due to the fact that diffusible substances might enter the body cells directly and would require the intervention of no antibodies whereas nondiffusible

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, June 8, 1931, Philadelphia.

substances require the action of antibody before they can be absorbed by cells. The work of Landsteiner[3] in which he shows that the specificity of a serum protein might be definitely changed by combination with organic, or even inorganic, radicals has been offered as an explanation on the assumption that there is a union of the nonnitrogenous substance with some protein of the body, and that this nitrogenous combination then served as an antigen.

The latter two hypotheses have a great deal to recommend them but, in the present state of our knowledge, nothing definite can be determined as to the accuracy of either. To the separate classification of these substances because of the lack of antibody in allergy due to nonnitrogenous substances, two objections may be raised. First, a not inconsiderable number of persons, classed as truly allergic, show no antibody in their blood. Second, the antibody, which is found in allergic persons, has not been proved beyond question to be the cause of the allergic reaction. If allergic individuals may show a continued absence of antibody although they exhibit frequent allergic reactions, and if the antibody may appear long before the clinical manifestations of allergy, or remain long after their disappearance, it is difficult to believe that the allergic reaction depends upon the presence of the antibody, and hence the mechanism of the allergic reaction must be an antigen-antibody reaction. Conversely, it seems hazardous to refuse to class as allergic those reactions in which antibodies cannot be shown to have a part.

If one admits the nonnitrogenous excitants of reactions into the allergic group, he may assume that both protein and nonprotein substances may participate in these reactions, or that the whole question of the substances which may react in this manner is open for investigation.

In studies upon pollen to determine its antigenic activity four methods of testing have been used and four different criteria adopted.

1. The production of skin reactions in sensitive persons or in passively sensitized sites.

2. The production of anaphylactic reaction either as determined by illness, or death, of the injected animal, or by the Dale test.

3. Treatment of sensitive persons by the use of specific substances.

4. The production of symptoms in sensitive individuals which symptoms duplicate those found in clinical allergy.

To the use of skin reactions as the criterion of antigenic activity is the possible objection mentioned above, namely, since the skin test does not always parallel qualitatively and quantitatively the sensitiveness of the individual, there is the possibility that skin reactions may not be produced by the pollen fraction which causes the clinical symptoms. Under ordinary circumstances there is sufficient parallelism to make the skin reaction a satisfactory test for sensitiveness, but, like

the Wassermann test in syphilis, this may be valuable as a diagnostic measure but undependable as a means of proving the relationship of a given pollen fraction to clinical sensitiveness.

The same objection may be raised to the use of the anaphylactic reaction to establish the identity of the reacting fractions. Reactions are to be expected in animals injected with sufficient protein, but the fact that animals react to this protein does not necessarily offer any evidence that clinical allergy is due to the same protein substance.

Successful treatment of allergic individuals by certain pollen fractions should be a fairly satisfactory method of determining the specific fraction in pollen, although one has to keep in mind the possibilities of nonspecific results and the question as to whether treatment is specific desensitization.

The reproduction of allergic symptoms in the sensitive person would appear to be the most dependable method of determining the specific factor. It is not subject to the objections brought against the use of skin tests and anaphylactic reactions, and it is, probably, susceptible of more accurate control than is use of the material in treatment.

In 1912 Schloss[4] used the individual proteins of egg white with which to test children. He found the skin reactions to be specific and destruction of the protein caused loss of reactivity.

Clock[5] in 1917 found that he could produce complement binding substances by injecting pollen into rabbits and suggested the use of the complement-fixation test as a means of standardizing pollen extract.

In 1917 Wodehouse[6] found different protein fractions in horse dander, cat and dog hair and Walker[7] found them to react specifically when used in skin tests.

In 1921 Parker[8] injected guinea pigs intraperitoneally with large amounts of ragweed pollen and secured Dale reactions with sensitized uteri. In 1924[9] she was able to produce precipitins in rabbits to ragweed pollen.

Huber and Koessler[10] in 1925 were able to sensitize guinea pigs to ragweed pollen as shown by the Dale method. Rabbits, also, were sensitized, and by passive transfer their sensitiveness could be passed to guinea pigs. This rabbit serum showed precipitin reaction.

In 1926 Longcope, O'Brien and Perlzweig[11] stated the active principle of horse dander to be in the protein and not in the nonprotein and lipoid fractions. Using the Dale method they found reaction to two fractions. These gave biuret reactions and contained most of the nitrogen. Two fractions containing little nitrogen gave little reaction. Skin tests were obtained with all fractions. O'Brien[12] reported passive transfer tests using an acid precipitate and an alkaline filtrate (the first rich in protein, the second very poor) and secured specific reactions with each.

In this same year Caulfeild, Cohen, and Eadie[13] separated four fractions from ragweed, timothy, and birch pollen. Guinea pigs were sensitized by the albumin-proteose and proteose fractions and this sensitiveness could be transferred to normal pigs. Skin tests were obtained which were apparently specific and treatment of pollen-sensitive patients with these fractions yielded excellent results.

Bernton, Jones, and Csonka,[14] also, separated from timothy and ragweed pollen four fractions which apparently reacted specifically in skin tests in sensitive patients and which they thought gave excellent results in treatment.

The work reported may be summarized thus:

Laboratory animals have been sensitized by injections of pollen extract as demonstrated by formation of precipitins and complement binding substance and by the Dale test. This sensitiveness can be passively transferred.

Fractions containing different proteins, or combinations of protein, can be separated from egg white, animal hairs and pollen. These showed antigenic activity and specificity when used in skin tests and by the Dale method and gave superior results in treatment.

In 1923 Grove and Coca[15] found pollen digested by trypsin and dialyzed showed an absence of protein as determined by the usual qualitative tests and no loss of activity as shown by skin tests. They suggested the possibility of the active substance being an enzyme.

Black[16] in 1925 repeated the work of Grove and Coca and secured the same result. He, also, did nitrogen determinations on pollen extracts and found that they gave no indication of the antigenic activity of the extract. Complement fixation was found to be lost after digestion of the protein but the activity as measured by skin reaction was not affected. Enzymatic activity was apparently ruled out. It was suggested that the active substance might be a polysaccharide, such as had been found by Heidelberger and Avery[17] in pneumococci. Black used intranasal instillation as a method of testing, believing it to be free of the objections which might be raised to skin tests and because it duplicated, as near as may be, the clinical reaction to pollen.

Black and Moore[18] reported a series of patients successfully treated with a 2 per cent ragweed pollen extract which did not give the usual qualitative reactions for protein. Alles[19] objected to the designation of "protein-free" to this extract. Tests made by him on this extract showed a difference between the total and nonprotein nitrogen (protein-nitrogen) corresponding to a dilution of a little more than 1-10,000. One patient in this series was given a subcutaneous injection of 0.1 c.c. of a 1-10,000 dilution made from this 2 per cent extract and had a prompt and severe systemic reaction. Calculation shows that she received one twenty millionth of a gram of protein. If this reaction, occurring in a woman of about 150 pounds in weight, as a result of sub-

cutaneous injection, can be ascribed to the protein present in such minute amounts, one must recognize in allergic persons a sensitiveness much greater than that shown by any sensitized laboratory animal.

Armstrong and Harrison[20] in 1924 found no relation between the complement binding power of pollen extract and the ability to produce skin reactions.

In 1923 Zinsser and Parker[21] working with tubercle bacilli and Heidelberger and Avery[17] using pneumococci, found a nonprotein residue in these organisms which reacted specifically with immune serum and proved to be a complex carbohydrate. These observations have been extended and soluble specific carbohydrates found in many other organisms and even in other substances. The finding that these substances, while not able to stimulate the production of antibodies, react specifically in high dilution with preformed antibodies, that they are capable of producing anaphylactic reaction in sensitized animals,[22] that they may produce skin reaction in sensitized persons,[23] and that the specificity of conjugated proteins depends upon the carbohydrate radical,[24] all have tended to show that carbohydrate substances may be shown to be responsible for phenomena which, in the past, have been attributed only to protein.

Stull, Chobot and Cooke[25] in 1930 found two substances in pollen, one of which appeared to be a polysaccharide and marked skin reactions were obtained in the majority of sensitive persons tested.

Recently Black[26] has reported the finding in ragweed pollen of a substance which does not give the usual protein reactions, does show the Molisch reaction and, after hydrolysis, shows marked reduction. The nitrogen content was 6.0 per cent and 5.2 per cent respectively in two separations. This substance, apparently a polysaccharide, gave typical skin reactions to ragweed-sensitive persons, no reactions in non-sensitive persons and, instilled into the nostril of a sensitive individual, produced typical symptoms.

The results obtained by the last mentioned observers may be summed up thus:

The activity of pollen extract does not depend upon the amount of nitrogen present.

Digestion of at least the greater part of the protein content of pollen extracts does not appreciably affect their activity.

Complement-fixation tests may serve as a means of determining the specificity of the protein present in pollen extracts but do not parallel their allergic activity.

A carbohydrate complex has been found which appears to react specifically.

These findings do not correspond very well with those previously mentioned regarding the use of separate protein fractions. They certainly would appear at first thought to be directly antagonistic. The

objection has been raised to the work of Grove and Coca, and of Black that there may remain some protein in the so-called "protein-free" extracts. It may now be equally pertinent to remark that there may be some carbohydrate remaining in the protein fractions. Certainly, the work done upon carbohydrate substances in bacteria demonstrates their immunologic importance. The findings in pollen extracts suggest their possible importance here also. Further work is certainly indicated if this apparent *impasse* is to be resolved.

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DISTRIBUTION AND IMPORTANCE OF THE PAPER MULBERRY *(PAPYRIUS PAPYRIFERA KUNTZE)* AS A CAUSE OF HAY FEVER AND ASTHMA IN THE UNITED STATES*

RAY M. BALYEAT, M.D., AND HERBERT J. RINKEL, M.D.
OKLAHOMA CITY, OKLA.

DURING the last five or six years we have examined many patients from Louisiana, Arkansas, southern Missouri and eastern Oklahoma who suffered from a severe form of seasonal hay fever and asthma during the latter half of April and the first half of May. Some of these patients were sensitive to the pollen of oak or grass, or both, but the treatment based on such findings did not give relief. Others showed no reaction to any of the common spring or early summer pollen. We were at a loss to know the cause of their symptoms. In the summer of 1928 Bernton[1] reported three cases of seasonal hay fever and asthma due to the paper mulberry. Before his report, and since, there has been no mention in the literature concerning this tree as an etiologic factor in seasonal hay fever and asthma. From that time on we began to study the distribution of the paper mulberry. We found it in very common use as a shade tree in our own city, and the following spring we were able to collect a small amount of pollen. Since that time we have used the paper mulberry pollen routinely in testing patients coming from various sections of the United States, especially those coming from the southeastern quarter. We have found 18 cases definitely sensitive. Knowing that a patient must come in contact with the pollen before he can possibly become specifically sensitive led us to believe that the tree is fairly abundant in certain villages and cities, and widely distributed. A questionnaire relative to the distribution was sent to the professors of botany of all the universities and agricultural colleges, and to the state foresters. Every state except Arizona responded. The map shown in Fig. 2 shows the relative distribution of the paper mulberry in the United States.

DISTRIBUTION OF THE PAPER MULBERRY IN THE UNITED STATES

In the southeastern quarter of Oklahoma we have found the paper mulberry tree cultivated for shade in practically every village and city. In some villages its growth is very abundant. In Oklahoma City during the last four or five years many trees have been planted around homes and in parks for shade. There has always been an objection to the red and the white mulberry on account of the fruit dropping on the sidewalk, but the paper mulberry is highly recommended by the nurserymen as a shade tree because it is fruitless, since only the male tree is sold. The Botany Department of the University

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

of Arkansas, at Fayetteville, reports the tree to be cultivated extensively as a shade tree in many of the towns throughout that entire state and that it grows wild along some of the ravines where there is plenty of moisture. The state forester of Missouri informed us that it was a common shade tree in the older towns and in the plantations of southeastern Missouri in the Mississippi flood plain, south of Cape Girardeau and east of Poplar Bluff. Mr. V. H. Sonderegger, state forester of Louisiana, reported the tree in New Orleans and Florida parishes. A botanist in Louisiana to whom we sent a questionnaire stated that he knew of no paper mulberry trees in the state but made the following comment:

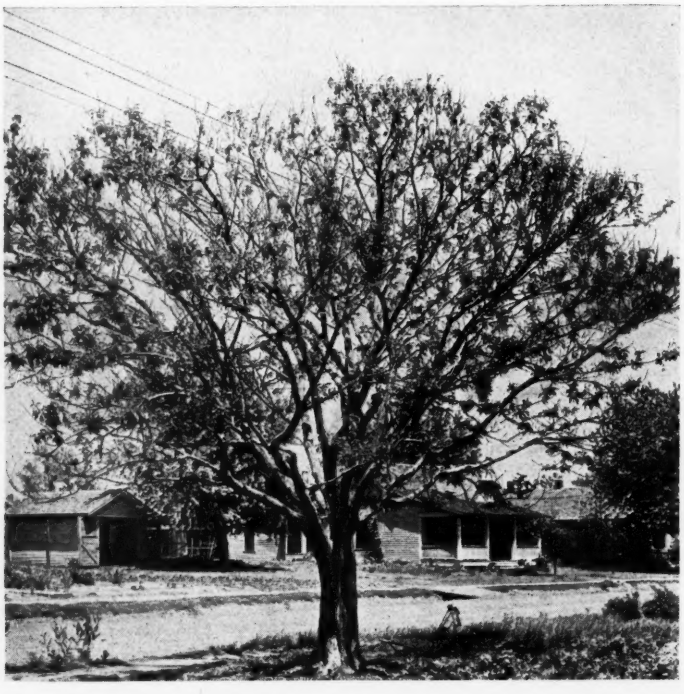

Fig. 1.—A pollinating paper mulberry tree near a home in a small mountain village in Arkansas.

"There was a mulberry tree here in town that acted very peculiarly, and people claimed that the tree was smoking. I did not examine the tree for its botanical species, but found the so-called 'smoking mulberry' was nothing but the gusts of pollen being emitted from the flower. I therefore spoiled a little hysteria, as the residents figured that something went wrong with the tree due to the so-called emission of smoke."

In traveling over the states of Louisiana, Arkansas, southern Missouri and eastern Oklahoma our observation has corroborated the reports from the botanists and foresters of the states mentioned.

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Plate I.—Enlarged motion picture frames illustrating the explosive character of pollination of the paper mulberry. The amount of pollen discharged from the anther by each unfolding stamen is sufficient in quantity so that the cloud of pollen can be seen for a number of feet as it drifts from the catkin. Since many flowers are exploded at the same time it makes the tree appear to be smoldering.

UNIV. OF MICH.

The tree is reported to be found occasionally in eastern Kansas and Texas. Prof. George M. Armstrong, of Clemson College, South Carolina, informed us that it grows extensively all over the state, especially around barns and neglected yards. Prof. B. W. Wells of West

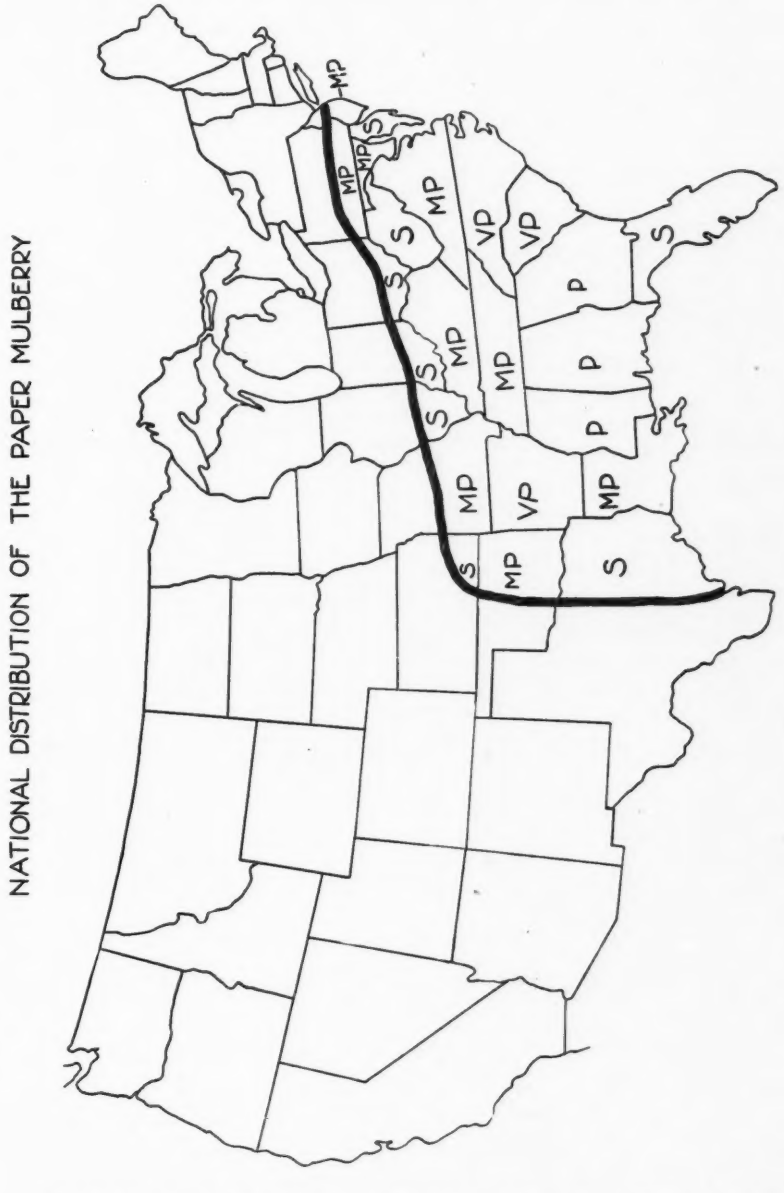

Fig. 2.—Map showing the distribution and relative abundance of the paper mulberry (*Papyrius papyrifera Kuntze*) in the United States.

Raleigh, North Carolina, finds it fairly common throughout that state. It is found, but not very extensively, in old and West Virginia. Bernton[1] reports many trees in the city of Washington, and he remarks that they seem to prefer vacant lots and yards and abound in alleys.

The map in Fig. 2 shows the extent of the growth of the paper mulberry in the states not specifically mentioned.

BOTANY OF THE PAPYRIUS PAPYRIFERA KUNTZE

The paper mulberry tree is deciduous in type. It does not often attain a height greater than 40 feet. The tree is called "paper mulberry" from the fact that paper of very good quality is made in China and Japan from its inner bark. The leaves are very large and beautiful. They are mostly egg-shaped, thin, toothed nearly all

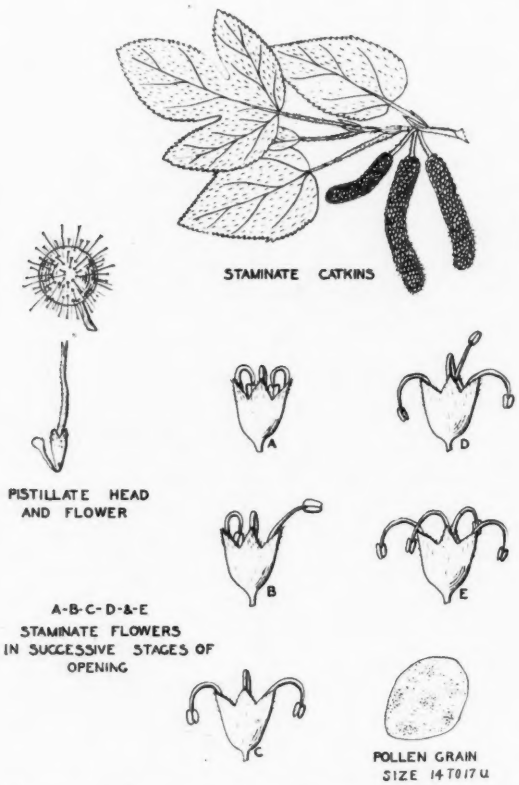

Fig. 3.—Drawing showing the male plant, staminate and pistillate flower, and pollen of the *Papyrius papyrifera Kuntze.*

around, and often deeply three-lobed, sometimes with a lobe on one side only. They are rough above, woolly beneath, ⅜ inch long. The spikes of the staminate flowers are ⅔ inch long. The heads of the pistillate flowers are ½ to 1 inch in diameter.[2, 3] The pollen is from 14 to 17 microns in diameter.

TOXICITY OF POLLEN

It has been our experience in dealing with the specific reactions that the pollen from one grass may be very toxic compared with that from

another. This is likewise true of the pollens from other botanical groups. Of the trees the pollen of the paper mulberry seems to be the most toxic of all. Experimentally, skin reactions are very large. Clinically, all cases we have seen with mulberry hay fever also have asthma.

We have two patients suffering from perennial asthma and hay fever who are sensitive to many pollens and animal epithelium, whose hay fever and asthma we have had no difficulty in controlling by

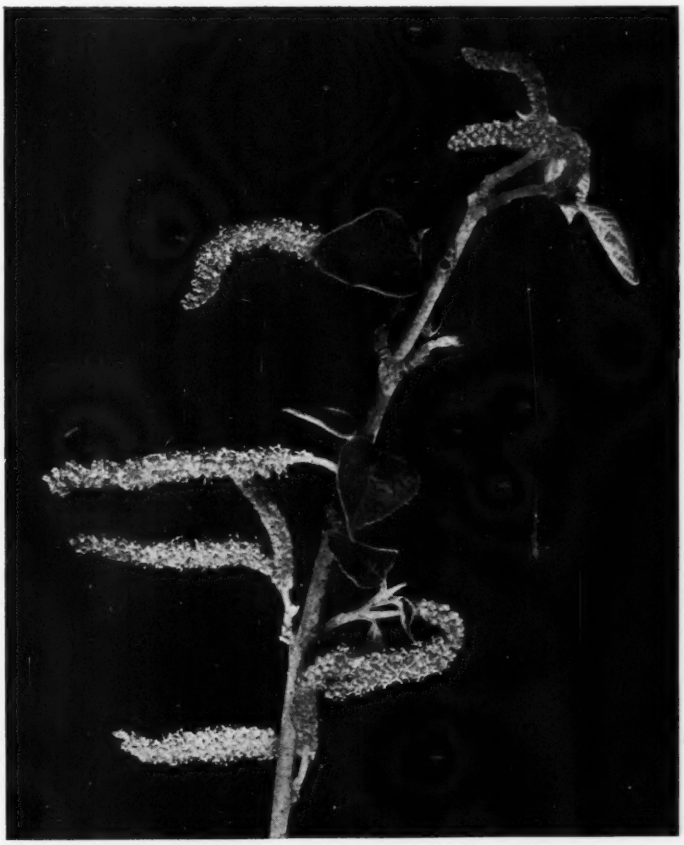

Fig. 4.—Paper mulberry catkin. The flowers on the catkin which appear light in color are those which have already exploded.

eliminative means and specific desensitizing to the pollens to which they are sensitive, except during the paper mulberry season. The paper mulberry pollen, however, has not been used in treatment because we have had difficulty in obtaining a sufficient amount of pollen for treatment material until this year. The severity of the asthmatic symptoms during the paper mulberry season has been so marked that both cases have had to seek a territory where the tree does not grow.

ORIGIN OF THE TERM "SMOKING MULBERRY"

Professors of botany and foresters from every state of the Union except Arizona kindly answered in detail our questionnaire. The question "Have you ever observed the peculiar method the mulberry tree uses in discharging its pollen into the air?" was answered by all. None had observed anything unusual about the mulberry tree during the period of pollination, but most of them stated that they had paid but little attention to the tree during that period. Two reported that the natives had called their attention to the fact that just before leaf-

Fig. 5.—Reaction from paper mulberry pollen by scratch method.

ing the twigs seemed to smoke, as if they were burning, and referred to the tree as the "smoking mulberry."

The latter part of April this year two asthmatic patients came to our clinic from Arkansas, one from the central and the other from the eastern portion, near the Mississippi River. Both believed that the mulberry tree was the cause of their present asthmatic symptoms. One of them told us about the peculiar action of this tree and also called it a "smoking tree," and insisted very much on our going over to see it, as she thought it would be of great interest. Dr. Rinkel and I drove 273 miles after working hours one Saturday evening and found on observing the tree the following morning, just as the sun was shining through the twigs, a most unusual phenomenon. It ap-

peared as if two or three hundred miniature people might be sitting in the small branches of the tree puffing smoke into the air. Several good sized limbs of the tree were brought back with us to our laboratories where a careful botanical study was made by our botanist. We found each catkin to be made up of from one to three hundred unfolded flowers, each of which consisted of four stamens folded in such a way that the flowers were round. By throwing artificial light on the plant the anthers of the flowers one by one would suddenly unfold with such force that a bag of dry pollen of sufficient amount would be thrown into the air so that it would be quite visible. The pollen was so extremely light that instead of settling to the table top, as in case of the usual pollen, it would gather on the ceiling of the collecting chamber.

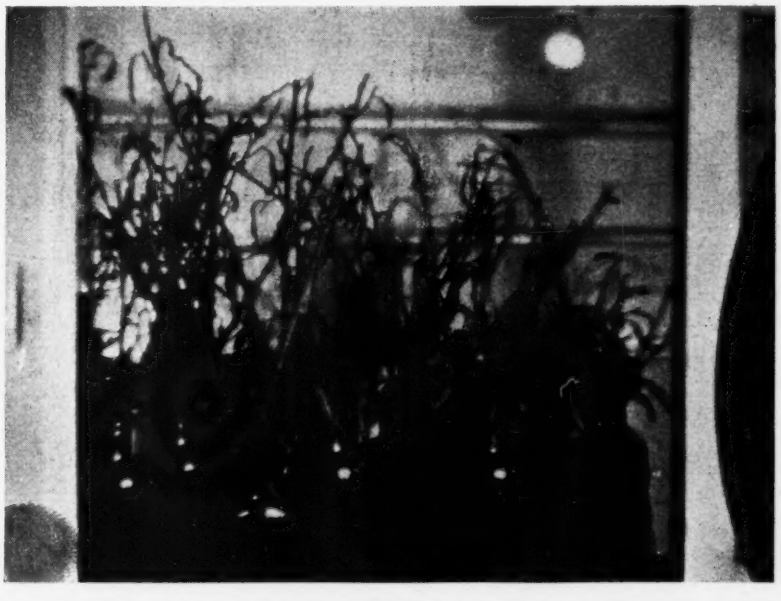

Fig. 6.—Glazed tile-lined chamber in which paper mulberry pollen was collected.

METHOD OF COLLECTING POLLEN

We found that the usual method of collecting pollen was not very satisfactory in the case of the paper mulberry, as the pollen is shot from the anther into the air with very great force by the stamen, when it suddenly unfolds, and being so extremely light it does not settle, as is the tendency in case of most pollens. In the collecting chamber we found our pollen to stick on the ceiling instead of the floor. We obtained our pollen by scraping the chamber top with a razor blade, instead of sweeping the floor with a camel's hair brush.

While in Arkansas in a little town where there were several hundred trees, we offered a retired business man $5.00 an ounce for all

the pollen from this tree that he would collect and send us. He laughingly said that we had better have our bank supply well arranged because he knew he could collect enormous quantities of the pollen. After two weeks' careful work with the various means of collecting which we outlined for him, and other means which he contrived himself, he sent us in a very large package a small ampule containing 1.25 grams, and in the package was a large card, marked "Valuation $1,000,000.00." We mention this to show the difficulty with which the pollen is obtained.

THE IMPORTANCE OF THE PAPER MULBERRY AS A CAUSE OF SEASONAL HAY FEVER AND ASTHMA

Papyrius papyrifera Kuntze has been cultivated in the United States for more than a century and a half, but the last couple of decades the nurserymen have pushed the sale of this mulberry throughout the small villages, towns and cities of the southeastern quarter of the United States, since people objected seriously to the red and white mulberry on account of their fruiting. The nurserymen soon learned that the paper mulberry puts out many sprouts and that these could be transplanted. Sprouts coming from the male tree naturally will produce a male tree. They were therefore able to offer to the public a nonfruiting mulberry tree. There are no doubt some pistillate trees in the country, but we have been able to find none. Thus practically all the paper mulberry trees in the United States are pollinators and therefore are possible hay fever and asthma producers. The amount of pollen these trees produce compared with the average tree is enormous, and is the lightest of all tree pollen. It is ejected into the air and therefore does not have a tendency to settle to the ground and become wet and deteriorate. We notice in our study that the trees grow not only in the front yards but many of them along the side of the homes very close to the bedroom windows. Around the home from which one of our patients came there were 17 male paper mulberry trees. The proximity of the tree to the home and the method by which the pollen is liberated expose patients to heavy concentration of the pollen.

During the last two years we have seen 11 patients with asthma and hay fever who were clinically sensitive to mulberry pollen. We have had many cases of seasonal hay fever and asthma during the last five years from the territory where this mulberry tree is abundant, whose symptoms correspond to the date of its pollination. Although we have not had an opportunity to recheck some of them, we naturally believe, from their history, that the mulberry pollen has something to do with their symptoms. From our recent botanical survey we find that the tree is used rather extensively for shade in the southeastern quarter of the United States.

Knowing what we do about the tremendous amount of pollen the tree produces and the degree of toxicity, and also knowing that patients who are born with the ability to become sensitive have a tendency to become sensitive to pollen that they come in contact with in massive doses, we are led to believe that many patients living in the southeastern section of the United States are sensitive to the pollen of the paper mulberry tree and that it is playing a part in the cause of their hay fever and asthma. It must at least be considered a possible etiologic factor in cases of seasonal hay fever and asthma whose symptoms occur during the late tree and early grass period, if they live in the territory in which this plant grows fairly abundantly.

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(For discussion, see page 97.)

STUDIES IN PASSIVE TRANSFER*

4. RECTAL ABSORPTION OF THE ANTIGEN (EGG WHITE)

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IN VIEW of the interest in allergic as well as physiologic phenomena, the question of colonic absorption is important. This report presents data obtained in a study of that question.

The products of protein digestion in vitro differ from the original protein by being slightly diffusible. For some time it was assumed that only diffusible protein was absorbed and hence that peptonization was essential. Schloss and Worthen,[1] however, demonstrated by precipitin and anaphylactic tests, that foreign protein might be absorbed in an undigested or partially digested state. This has been more recently confirmed by Walzer[2] by application of the local passive transfer phenomenon described by Prausnitz and Küstner.[3] Walzer showed that, in adults, oral administration of the antigen gave results quite comparable with those obtained by injection in the local sensitized skin areas. In a previous study[4] we have reported similar results in newborn infants.

There has remained, however, the question as to the site of this absorption in the intestinal tract. The opinion in many textbooks is that absorption takes place above the cecum and that only water and crystalloids are absorbed from the large bowel. The contrary evidence of Voit[5] has apparently been overlooked. Following rectal administration of egg white and salt solution, they found an increase in urinary nitrogen. Since it was known that practically no peptonization took place in the colon and since the effect of enzymes could be ruled out, absorption probably accounted for their findings. Egg white represents a nonassimilable type of protein in contrast with its acid albumin fraction. Introduced in the blood stream the former substance is excreted by the kidney. Schloss and Worthen[1] demonstrated the presence of egg white in the urine following oral administration. They emphasized the greater absorption from upset or abnormal intestinal tracts. Colonic absorption is suggested from their findings since with increased peristalsis the chance of absorption from the upper intestinal tract is less. Yet it has been shown by previous passive transfer studies[4] that the majority of healthy young infants will absorb egg white antigen after oral administration. The following experiments were designed to see if application of local passive trans-

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fer technic would give evidence of colonic absorption in normal infants and rule out the possible effect of digestive processes in the upper intestine.

PROCEDURE

Blood was taken from a patient, B. B., who gave markedly positive skin tests to egg white. Part of the sample was sent for a Wassermann test which was reported negative; the rest was centrifuged after clotting and the supernatant serum was removed. This was first tested on controls who gave the characteristic local passive transfer reactions.

Infants in the nursery (ages three to seven days) were then selected as recipients, after a very careful search had revealed no familial allergic history. One tenth c.c. of the anti-egg serum was injected intracutaneously on the flexor surface of the forearms. After forty-eight hours allowed for sensitization of the local skin area, the infants were given a colonic flush. The antigen solution was then prepared by shaking about 15 c.c. of egg white with 300 c.c. of distilled water. After passage through a Seitz filter to assure sterility, the mixture was ready for injection.

The first injections of 15 to 30 c.c. given at once were promptly expelled and the reactions were not uniform. Subsequently it was decided to inject more slowly. A No. 18 F. catheter was attached to a 30 c.c. luer syringe filled with the antigen mixture and 2 to 3 c.c. were

TABLE I

PROTOCOLS

NAME	SERUM INJECTED AGE IN DAYS	ANTIGEN GIVEN AGE IN DAYS	TIME REACTION APPEARED	WHEAL CM.	ERYTHEMA CM.
Baby					
1	7	9	1 hr.	3 × 4	10 × 12
2	5	7	45 min.	4 × 6	8 × 8
3	5	7	40 min.	6 × 7	10 × 12
4	5	7	1 hr.	4 × 8	14 × 10
5	6	8	35 min.	10 × 10	12 × 14
6	6	8	1 hr.	4 × 6	10 × 10
7	4	6	30 min.	10 × 12	20 × 20
8	4	6	30 min.	8 × 6	10 × 14
9	3	5	1 hr.	8 × 6	8 × 8
10	3	5	40 min.	30 × 25	40 × 5
11	10	12	40 min.	20 × 24	40 × 40
12	5	7	20 min.	12 × 16	40 × 40
13	3	5	35 min.	10 × 12	20 × 20
14	3	5	1 hr.	8 × 10	20 × 30
15	3	5	30 min.	6 × 8	10 × 10
16	7	9	30 min.	10 × 14	Whole lower arm
17*	7	9	1 hr.	?	5 × 7
18	6	8	20 min.	10 × 12	40 × 30
19	6	8	1 hr.	14 × 12	20 × 20
20	6	8	1 hr.	10 × 12	Whole lower arm

*Patient was jaundiced, had diarrhea on day antigen was injected. Probably impossible to retain antigen.

injected at intervals of two to three minutes until 20 c.c. had been given. The whole procedure took about fifteen minutes. While some of the antigen solution was expelled around the catheter, most of it was retained. In order to be sure that the solution was limited to the colon, barium was injected with the solution in two of the recipients and roentgenograms were obtained.

RESULTS

Since the reactions following the sensitizing serum injection had completely subsided and in some patients the site was almost undetectable, no control skin injection was needed. Reactions consisting

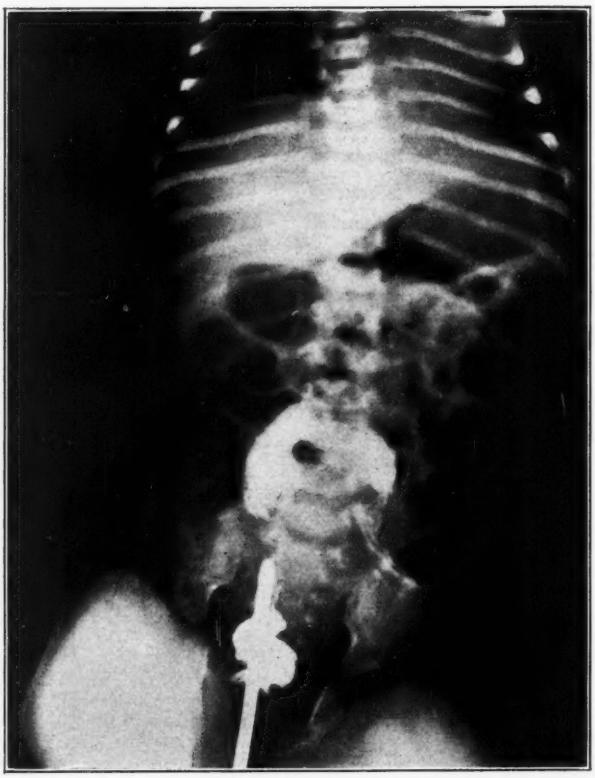

Fig. 1.—Abdominal x-ray plate of Baby 12, age seven: shows the barium extending up as far as the middle of the sigmoid loop.

of wheal formation and erythema appeared as soon as twenty minutes after injection in some cases; in others it did not appear until one hour. The average lapse of time was thirty-five minutes. The reaction varied somewhat in intensity but was usually most striking. In one patient there was considerable swelling around the local site which did not subside until four hours later. One patient gave only erythema formation without a wheal. Diarrhea had been present antedating the rectal injection, and it was thought that more of the anti-

gen solution had been expelled. That it was not the result of failure to give passive transfer was shown by the prompt response on oral administration. Table I presents the results on 20 consecutive infants.*

CONCLUSIONS

It can be shown by local passive transfer technic that the colon of normal young infants will allow passage of egg white antigen. The absorption may be confined to the lower bowel and is evident in twenty to sixty minutes. It would hence appear unlikely that digestive processes have any effect.

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*These infants are being followed to see if, in the absence of evidence of hereditary allergic trend, the early introduction of raw egg white will result in any hypersensitivity to the substance or in any permanent skin reactions.

XI. A DRY POLLEN OPHTHALMIC TEST IN POLLEN ASTHMA AND HAY FEVER PATIENTS NEGATIVE TO CUTANEOUS TESTS*

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THE literature is replete with communications dealing with many phases of hay fever and asthma due to pollen sensitiveness. Almost all workers in allergy have stressed the cutaneous tests (scratch and intradermal technics) as the sole means of determining the exciting or causative factors of pollen sensitiveness. This has resulted in the classification of a significant number of patients as non-sensitive to pollen in spite of the fact that histories consistent with pollen as the etiologic factor were elicited.

Patients with typical pollen asthma and hay fever in whom the results of the sensitization skin tests were negative have been experienced by Piness,[1] Kern,[3] Vaughan[2] and others. Kahn and Grothaus,[4] however, were the first to emphasize the important rôle that pollen played in seasonal asthma in patients who showed negative intradermal reactions to a 1 to 20 solution of pollen extract. Thirteen per cent of their series of 115 patients of all ages with pollen asthma were classified as refractory to the cutaneous tests. Kahn and Grothaus introduced a diagnostic test which involved subcutaneous injections of serial dilutions of pollen extracts. They had no experience with the conjunctival test. In 1926, working independently of Kahn and Grothaus, I[5] advocated after an experience of four years, a simple and harmless eye test with natural pure pollen for patients refractory to the skin tests. An incidence of 7 per cent of 100 children with asthma living in New York City was reported.

The use of the conjunctival sac as a means of testing with pollen has been almost entirely restricted to serial dilutions of pollen extracts. The patients tested were those already showing positive reactions to pollen with the cutaneous technic. Cooke[6] and Vander Veer[7] have applied the conjunctival test particularly for the determination of the degree of hypersensitiveness to pollen and so classified cases of hay fever into specified groups which according to Fineman[8] could not be determined with any degree of accuracy. These authors have also demonstrated that stronger solutions of pollen extracts were required to elicit positive reactions with the conjunctival than with the

*From the Children's Asthma Clinic, Mt. Sinai Hospital, Department of Pediatrics.
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intradermal method. The studies on pollen carried on by Bernton[9] have served to establish skin sensitiveness and mucous membrane sensitiveness as two distinct entities.

Scheppergrell[10] used the dry pollen eye test (his so-called biologic test) in patients positive with the cutaneous method merely to induce symptoms of hay fever.

Walker[11] and Balyeat[12] in their recent works do not make mention of any eye tests.

Duke[13] while only employing the conjunctival test with a dilution of pollen extract states that "it is not difficult to conceive that the exposed tissues might react to dry untreated pollen even though insensitive to pollen in high dilution." Rackemann[14] in his recent book argues that a concentrated solution of the suspected pollen dropped into the conjunctival sac is probably stronger than any solution of airborne pollen in the normal tears which may occur spontaneously, and negative results would appear to rule out an active sensitiveness. However, clinical experience has demonstrated that when a patient with pollen allergy shows negative reactions with the scratch method to dry pollen and with the intradermal method to a 1 to 50 or 1 to 20 extract the application of the corresponding dry pollen to the conjunctival sac will in a majority of instances show positive reactions. Moreover, the application to the eye of a 1 to 50 or 1 to 20 extract of pollen will invariably result in a negative reaction.

INDICATIONS AND CONTRAINDICATIONS

When the etiology of asthma or hay fever is obscure and a history suggests possible pollen etiology and the cutaneous test is negative, the conjunctival test with dry pollen should be employed. Under no circumstances should the eye test be performed when the scratch test shows a positive reaction. With the latter test any reaction larger than the control is regarded as positive.[15] If the intradermal technic is employed as a routine practice, the eye test to dry pollen can be performed after the patient has reacted negatively to serial dilutions of pollen extracts up to a concentration of 1 to 50. With the intradermal test only the two- and three-plus reactions are regarded as definitely positive.[16]

Patients with "vernal conjunctivitis" should not be subjected to the dry pollen eye test during the pollen seasons because of the danger of markedly aggravating the disease.

Patients with any inflammatory conditions involving the eye structures should not be tested because of the difficulty encountered with proper interpretation of reactions.

For the last several years the eye test with dry pollen of the trees, grasses and weeds has been routinely performed on patients with asthma, vasomotor rhinitis (perennial or seasonal) and vernal catarrh.

From these routine tests, as with cutaneous tests, some positive reactions were obtained which had no clinical bearing on the existing complaint and so were classified as potential factors of pollen allergy. There are a certain number of patients with pollen allergy from whom histories of intolerance are difficult to obtain. However, eye tests performed in a routine manner will often show reactions which when brought to the patient's attention, help to corroborate the diagnosis.

The eye test with dry pollen, properly performed, is simple and harmless. The test can be applied with relative ease to children as young as four years.

TECHNIC OF THE TEST

The pollen employed for these tests should be natural, properly prepared and dry. The lower lid of the eye to be tested is drawn downward sufficiently to expose the conjunctival sac. The patient is requested to look upward. A quantity of pollen equal to the amount used for a scratch test is dropped into the conjunctival sac from a small vial held between the thumb and index finger. The pollen is allowed to remain in the eye for at least five minutes during which time the patient holds the lids shut with a pledget of absorbent cotton. At the end of five minutes the pollen residue is removed from the eye with the aid of an applicator tipped with cotton. Gentle manipulation is employed when removing the pollen residue in order to avoid traumatism of the tissues. The appearance of the eye should be noted immediately before and after removing the pollen residue. Five minutes later the reaction is read and then one or two drops of epinephrin hydrochloride (1-1000 solution) is dropped into the eye. At the end of another few minutes the effect of the epinephrin is recorded. Fur-

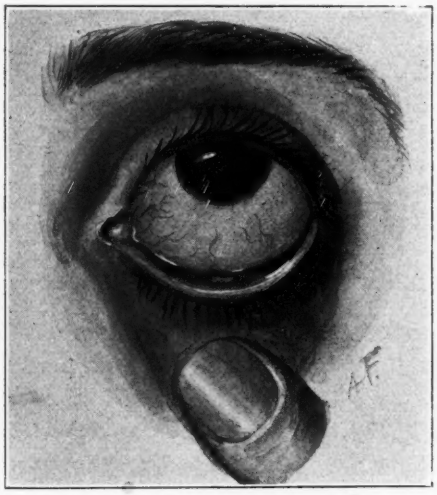

Fig. 1.—One-plus positive reaction.

ther application of epinephrin may be used to clear or control the congestion caused by a strong positive reaction. When a patient is tested for the first time and shows a positive reaction in one eye, the other eye should be controlled with pine pollen. Eyes are not retested the same day. Tests can be performed daily.

POSITIVE REACTIONS

One-plus reaction: The conjunctiva is moderately congested. The sclera is moderately red with the congestion more confined to the area immediately above the scleroconjunctival junction. The caruncle is only slightly reddened and swollen (Fig. 1).

Two-plus reaction: The redness of the sclera is more diffuse and intense than a one-plus reaction. The injection of the sclera is clearly

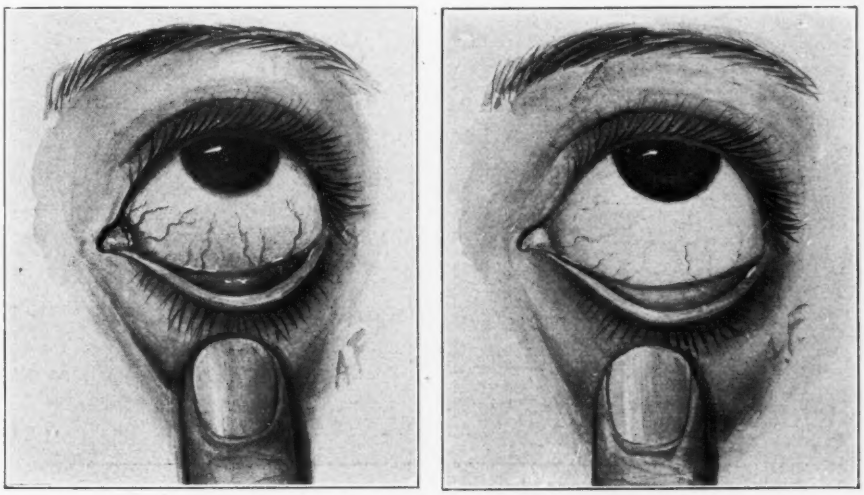

Fig. 2-*A*. Fig. 2-*B*.

Fig. 2.—*A*, Two-plus positive reaction. *B*, Two-plus positive reaction after the application of epinephrin hydrochloride (1-1000 solution). The reaction is entirely clear.

noted. The conjunctiva is moderately congested. The caruncle is moderately swollen and red (Fig. 2 *A*).

When the reaction is localized to the area on the sclera and conjunctiva where the dry pollen first came in contact, it is called a "blotch reaction" (Fig. 3 *A*).

Three-plus reaction: This reaction is similar to a two-plus reaction except that the degree of redness and the injection of all the tissues are more intensified (Fig. 4 *A*).

Four-plus reaction: In this type of reaction chemosis of the sclera, conjunctiva and caruncle of varying degrees is observed. The chemosis and not the redness is the diagnostic feature of this reaction. When the reaction is marked, the pupil appears embedded below the

surface of the sclera. The sclera becomes markedly edematous, which may assume the appearance of jelly-like masses (Fig. 5 *A*).

Delayed reaction: This type of reaction is recorded as positive and first makes its appearance from twelve to twenty-four hours after the eye test is performed. A delayed reaction assumes the appearance of either the one-, two- or three-plus immediate reactions. Delayed reactions are uncommon and may be looked for in patients suffering with vernal catarrh when tested outside the pollen seasons.

A patient with a three- or four-plus immediate reaction may have a persistence of symptoms ranging from several hours to forty-eight hours. The persistence of such symptoms is actually a continuation of the primary reaction, and should therefore not be confused with the delayed reaction.

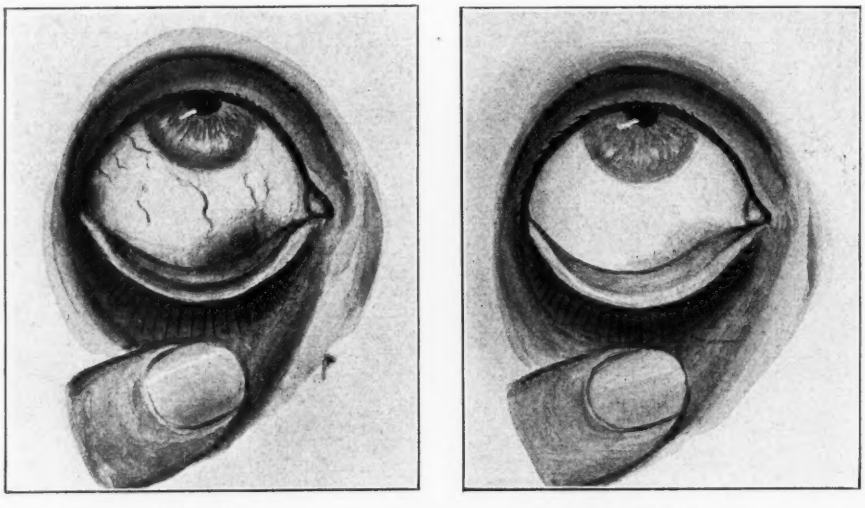

Fig. 3-*A*. Fig. 3-*B*.

Fig. 3.—*A*, Two-plus positive "blotch" reaction. *B*, Two-plus positive "blotch" reaction after the application of epinephrin hydrochloride. The reaction is not entirely cleared. This resistance to epinephrin is called a "positive epinephrin test" which speaks for a positive reaction—potential or etiologic sensitiveness.

SYMPTOMS ASSOCIATED WITH POSITIVE REACTIONS

Itching: Itching of the eye is confirmatory evidence of an existing positive reaction but is not to be considered an important symptom because absence of itching is observed to occur in many cases with strongly positive reactions.

Lacrimation: Watery discharge from the eyes with varying intensity especially occurs in a patient showing a three- or four-plus reaction and is a sign of no clinical importance.

Appearance of the eye: The eye showing a positive reaction ranging from a two to four plus appears definitely smaller than the controlled eye. The more intense the positive reaction the smaller the eye appears.

Nasal symptoms: One or all of the nasal symptoms of hay fever—watery discharge, sneezing, itching and blocking—may occur on the same side where the eye test shows a positive reaction. These artificially induced symptoms of unilateral hay fever may last for hours.

NEGATIVE REACTIONS

Plus-minus reaction: This reaction is less than a one plus and more than the control, and for purposes of record is regarded as negative.

Negative reaction: This reaction differs in no way from the control or the original appearance of the eye.

Traumatic reaction: The eye in many persons becomes reddened with the introduction of any foreign substance, even if the substance

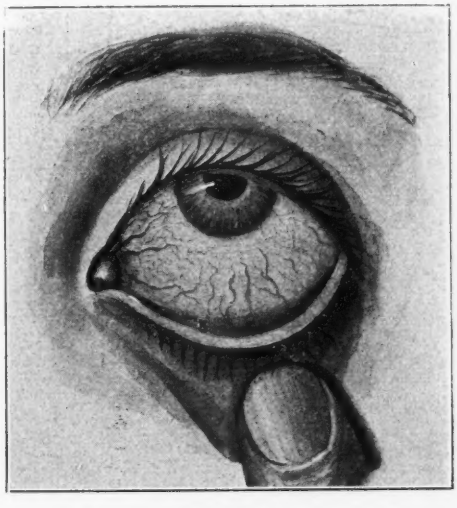

Fig. 4-*A*.

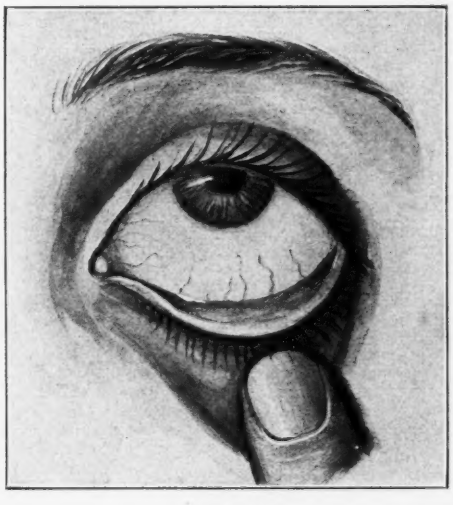

Fig. 4-*B*.

Fig. 4.—*A*, Three-plus positive reaction. *B*, Three-plus positive reaction after the application of epinephrin hydrochloride. A "positive epinephrin test" is present

be as clean as properly prepared dry pollen. A traumatic reaction prior to the removal of the pollen residue from the eye usually appears like a one- or two-plus reaction. After the pollen residue has been removed from the eye the congestion rapidly fades so that at the end of five or more minutes the eye is practically restored to its original appearance. A true positive reaction at the end of five or more minutes shows a persistence or an increase in the intensity of the original reaction. This fact is of diagnostic importance.

A slight burning sensation in the eye lasting for a minute is experienced by a majority of patients tested with the dry pollen of short and giant ragweed which frequnetly gives rise to a one plus reaction. This type of reaction occurs almost entirely with ragweed pollen and is recorded as negative unless proved otherwise.

Ophthalmographic reaction: Dermographia is too well known a condition to require description. The parallel of this irritation phenomenon is also found to occur in the eyes of certain persons on whom the dry pollen test is performed. The reaction usually appears like a three plus. All pollens including pine will show the same reaction. This condition is referred to as "ophthalmographia," a new term which I believe to be fairly descriptive of the condition. Ophthalmographia like dermographia, is not always constant in the same person.

Ophthalmographia differs from a traumatic reaction in that the congestion with the former shows no tendency to fade at the end of five or more minutes. The ophthalmographic differs from a true positive reaction of similar degree in that epinephrin hydrochloride (1-1000 solution) rapidly clears the former reaction and only controls the latter. This fact is diagnostically important.

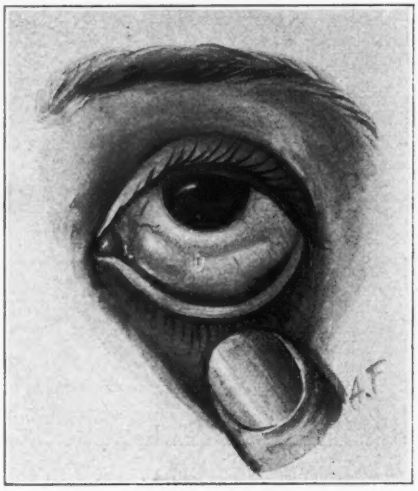

Fig. 5-*A*.

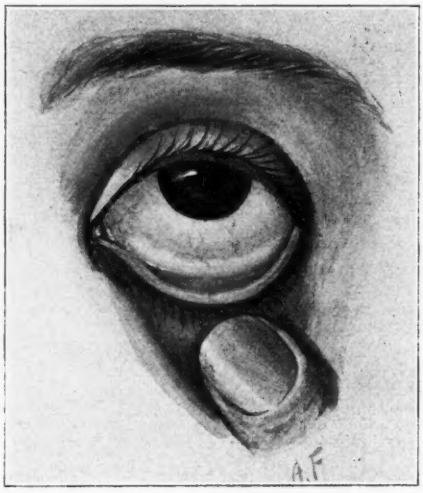

Fig. 5-*B*.

Fig. 5.—*A*, Four-plus positive reaction of marked degree. Chemosis and not redness is the diagnostic feature. *B*, Four-plus positive reaction after several applications of epinephrin hydrochloride. A "positive epinephrin test" always occurs with this type of reaction.

The application of epinephrin hydrochloride (1-1000 solution) to the eye is intended not only to control or clear the congestion of the mucous membrane and sclera resulting from a positive reaction to dry pollen but also to assist in the differentiation of the true from the pseudoreactions.

The condition of the conjunctiva and sclera caused by a one-plus reaction is always and rapidly cleared by one or two drops of epinephrin.

The congestion caused by a two-plus reaction is cleared in a majority of cases after the application of epinephrin (Fig. 2 *B*). In a small number of instances the pollen reaction resists to some degree the

clearing effect of epinephrin (Fig. 3 *B*). This resistance to epinephrin is called a positive "epinephrin test." A positive epinephrin test always speaks for a positive eye reaction to pollen—potential or etiologic sensitiveness—and is diagnostically important.

A positive epinephrin test is observed to occur invariably with a three-plus (Fig. 4 *B*) and always with a four-plus reaction (Fig. 5 *B*). Excessive application of epinephrin to the eye showing a four-plus reaction is inadvisable because entire clearing of the reaction does not take place. The edema and the blanching of the skin on and below the lower lid caused by the repeated use of epinephrin tend to annoy the patient more than the reaction to pollen itself.

The degree of reaction of a positive eye test bears no relationship to the severity of symptoms or type of pollen syndrome a patient may have. It can be stated, however, that the majority of patients with pollen allergy who are refractory to the cutaneous tests suffer from pollen asthma with or without hay fever. In other words, only a small number of patients with uncomplicated hay fever show the phenomenon of negative skin tests with pollen.

COMMENT

It is agreed that the nature of the symptoms of hay fever and pollen asthma lends itself to easy diagnosis. Such a diagnosis is confirmed by the positive reactions obtained to the suspected pollen with the cutaneous tests. It is also generally assumed that if these reactions be negative it is improbable that the case in question is one of pollen sensitivity.

Schloss[17] and O'Keefe[18] and many others reported patients with food allergy in whom protein sensitization was clinically demonstrated, with negative cutaneous tests. Rowe[19] emphasized the important rôle that this group played in allergy and introduced a system of "elimination diets" as a means of confirming the diagnosis. This method of diagnosing patients with food allergy and negative cutaneous reactions has now been generally accepted.

Extensive clinical experience has demonstrated that there also exists a group of persons with definite pollen allergy who for some unexplainable reason exhibit the phenomenon of reacting negatively to pollen with the cutaneous tests (scratch and intradermal technics). Moreover, it has been shown by Peshkin and Fineman[20] that specific reagins in the blood serum of such patients could not be demonstrated. As a means of confirming the diagnosis of pollen allergy in this group of patients, a simple and harmless eye test with natural, pure, dry pollen was suggested in 1926. In this communication I wish to reemphasize that the main purpose of the dry pollen eye test is to determine, not the degree of sensitivity, but, rather, the absence or presence of sensitization when skin sensitization is absent. Those

patients with pollen allergy, with special reference to the asthma syndrome, who are refractory to the cutaneous tests, comprise a group of persons sufficient in numbers to command the attention of all workers in allergy. The dry pollen eye test is now presented in such detail as to enable one to perform and interpret the test with ease and accuracy.

If I have given the impression that patients with symptoms of pollen allergy negative to the dry pollen eye test are to be ruled out as being pollen insensitive, I wish to state that is not correct. Kahn[21] has successfully treated a number of these patients with specific pollen injections. This type of patient can be referred to as being refractory to the eye test in contrast to those refractory to the cutaneous tests. The good results obtained by Kahn with pollen asthmatics refractory to the eye test have also been obtained by me but in a limited experience because the incidence of such patients living in New York City is extremely small.

Experience with the dry pollen eye test now extended over a period of nine years on a large number of patients tested during all seasons of the year and under varied conditions justifies the statement that this test will prove to be a reliable and practical contribution to the subject of allergy.

Future communications[22] will deal with many pertinent facts which do not come under the scope of this paper.

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(For discussion, see page 99.)

GLUE SENSITIVITY

GEORGE C. ANDREWS, M.D., AND CHARLES W. MCNITT, M.D.
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SEARCH has disclosed only a few reported cases of glue sensitivity in the literature and no reports of treatment with glue antigen.

CASE REPORT

Miss D. C., aged eighteen years, came to us with two chief complaints: (1) an intermittent swelling of the lips and tongue and, (2) asthmatic attacks when in the drafting room of her art school.

Present Illness.—At about the age of thirteen, and five years before seen, the patient began to have occasional attacks of coryza, swelling and itching of the lips, tongue and throat, and mild asthmatic wheezing, which lasted from a few minutes to a few hours. Sometimes there was an accompanying transient nausea. After several such attacks, it was observed that they frequently occurred a short time after eating codfish cakes on Sunday mornings. A typical attack is excellently described in the patient's own words: "After eating fish, in less than five minutes my tongue, lips, and throat start to itch. It is not a painful itch but very steady. My tongue becomes rough and swells, as do my lips. At the same time my eyes begin to itch and water and grow inflamed. I sneeze and my nose runs. In perhaps fifteen minutes I have felt, at times, an active nausea. At other times if a very slight amount of fish has been consumed, I feel merely upset. My stomach usually becomes settled after a dose of soda. In an hour the swelling of the lips and mouth has gone down. In an hour and a half I stop wheezing and feel quite normal except for my eyes, which stay inflamed and swollen for perhaps twenty-four hours." These attacks have been avoided by not eating fish.

For some years the patient has also found that contact of the lips and tongue with the adhesive of stickers, labels, etc., gave very much the same type of reaction; i.e., swelling and itching of the lips, tongue and throat, nasal and ocular catarrh, asthma and, at times, transient nausea. This was not noted with the ordinary United States postage stamps and envelopes but occurred with commercial labels, Christmas seals, and the like. These she had therefore learned to avoid.

About five months before first seen, at the beginning of the Fall term of her school, she began to have "asthmatic attacks" when in the drafting room. A stay of fifteen to thirty minutes in this room was always followed by such an attack. Sneezing, redness of the nose and

eyes, with lacrimation and watery nasal discharge initiated the trouble, followed by a difficulty in breathing of varying degrees of severity, usually mild and of short duration but productive of real discomfort. The eyes and nose were the parts most markedly affected and in one bad attack the eyes became swollen nearly shut in an hour, this swelling slowly subsiding during the next twenty-four hours. With these symptoms, no generalized urticaria or erythema developed. She was not nauseated. The only oral symptom was that of a slight puffiness of the lips.

Past History.—Measles, chickenpox, and whooping cough were the only childhood diseases. Appendectomy was done in childhood. She never had eczema, hives, or skin rashes of any nature before the onset of the present illness. The patient was otherwise an extremely healthy girl.

Family History.—On the paternal side, the father and uncle both have hay fever. The maternal grandmother had severe asthma and fish disagreed with her. Her mother's brother could not eat clams as a child but later outgrew this. A cousin on the maternal side has hay fever. The mother has had mild eczema and one brother has hay fever, being sensitive to horse dander. Two younger sisters are symptom-free. We have had no opportunity to study further these familial instances of allergy.

Physical Examination.—This showed no noteworthy abnormalities. The skin was entirely clear.

Skin tests with the scratch method were made against all common food, pollen, and ordinary epidermal allergens. All these were negative except in the group of fish protein where there was a marked reaction to codfish which we labelled 4 plus, a 3-plus reaction to bluefish, and a 2-plus reaction to salmon. These were confirmed at a future visit and tests were then made with the following substances: a commercial India ink, gelatin, and glue. The ink and gelatin were negative. The reasons for specifically using these products will be brought out in the discussion on the nature of glues.

A scratch test was then made, with a small quantity of Dennison's fish glue and at the end of five minutes there developed a wheal which rapidly grew to the size of one's palm with large irregular pseudopodia, and the patient began to complain of discomfort in breathing. The excess glue was immediately washed off with water and the patient was given 8 minims of 1:1000 adrenalin solution subcutaneously. For a period of half an hour there was a marked dyspnea and musical râles were heard throughout the lungs on auscultation. The blood pressure, taken after emergency measures had been cared for, was 130/80. The same dose of adrenalin was repeated in twenty minutes and at the end of an hour the patient had recovered from her asthma

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and, although feeling somewhat weak, was able to leave the office comfortably. We do not know the length of duration of the local wheal.

CASE REPORTS IN THE LITERATURE

There have been many reports of patients sensitive to fish protein. These are of interest but are too numerous to be taken up in this paper. For those who may be interested in the study of the problem and the relationship between the reactions of glue and fish, which we feel is well established, references to the case reported by Grutz[1] and to the work of Prausnitz and Kustner[2] are given.

In many places in the literature we have found references to glue as an allergen. In practically all of these, however, it was merely mentioned. Case reports are few. There were no results of treatment found. While two of the cases noted below specify fish glue, most references are made to glue as a general term, irrespective of its derivation.

Cooke[3] reported a case of death following an intradermal skin test with fish glue. This case had given a moderate reaction to ovo-mucoid and a marked reaction to egg-white globulin. It is interesting to us that tests to all meat extracts were negative. This we mention particularly because we feel that the reaction to glue is probably dependent upon its fish protein content and as far as we are able to discover does not follow any of the other animal glues. The same author reported another case in which coryza from ragweed pollen was established and also asthma and coryza from handling LePage glue. In this case, also, a marked constitutional reaction with almost immediate onset of symptoms followed the injection of the glue.

Another severe case of allergy due to fish glue was reported by Duke and Stofer.[4] In their case a scratch test proved nearly fatal. This patient, too, had had symptoms and at times collapse following contact with glue on stamps. At one time the wet label of a beer-bottle, at another, recently repaired shoes were responsible for severe attacks. Our case parallels theirs in the reaction to the scratch test with glue, except that ours was slightly less severe. Like their case, ours has suffered no ill effect from the reaction. The relief of their patient was accomplished by the removal of glue from his house.

During our investigations, a manufacturer of protein treatment sets personally informed us of several glue-sensitive cases. On all but one of these cases we have been unable to obtain the details. One concerned a worker in a leather goods and suitcase factory. In this case the development of wheals over the body had been noticed for a number of years. The fact that he can eat fish without symptoms causes us to doubt the authenticity of this case.

Another is the case of a boy who was working in a manual training room of a school and whose asthmatic attacks were traced to fish glue.

We are greatly indebted to Dr. H. A. Gilmartin[5] for the following personal communication, which gives us the only other available report of results of treatment by injections of glue solution.

A female child, ten and a half years of age, complained of asthma since the age of three. The family history was negative for allergy except for some attacks of urticaria in the mother. Infantile eczema was present in this case at the age of three months and lasted for a period of three years. Weight and development were normal. At the age of three the patient had attacks of vomiting, associated with headache and constipation. Between these attacks the mother noticed a running nose, cough, and some difficulty in breathing. Definite symptoms of asthma soon developed and symptoms, also, closely resembling the ordinary head cold. They appeared at short intervals and lasted from seven to ten days. Cough had always been a prominent symptom. Fish had been known to disagree with the child and skin tests had been reported positive for cocoa, apple, and pear by a Boston physician. Shortly before seen, adrenalin had become necessary to relieve the severe attacks of asthma.

On examination, the patient presented the picture of a chronic asthmatic; tall, thin, extremely pale, with a barrel-shaped chest. Wheezing was marked and audible across the room. Musical râles were present throughout both sides of the chest. Many skin tests were made and many clinical precautions observed, such as the removal of pet animals and birds, furs; the omission of silk from her wearing apparel, and the limiting of diet. The skin tests had revealed a moderate reaction to codfish and mackerel. A free interval was suddenly terminated upon handling a camera. This recalled a similar circumstance a short time previously which followed playing with a toy which was heavily glued. A history was then given of several attacks of watery, swollen eyes after "pasting" during school hours. The test for glue was finally made and the patient reacted with a large local wheal. There were no constitutional symptoms at the time of the test. This patient has improved under the schedule of treatments as given in Table I.

RESULTS OF TREATMENT

In the reported cases of glue sensitivity, treatment has consisted of removal of the substance from the environment of the patient. The case treated by Dr. Gilmartin and our case are the only ones in which records of treatment by subcutaneous injections of the extract of the allergen, fish glue, have been found. These series of treatments are outlined in Tables I and II.

In Case 1 the following observation was made nine months after the injections were started: "Patient has been free from asthmatic signs

TABLE I

CASE E. D. (PATIENT OF DR. H. A. GILMARTIN)

DATE	FISH GLUE EXT. DILUTION	SUBCUTANEOUS INJECTIONS (MINIMS)	REACTIONS
Jan. 17	1:200,000	1	
Jan. 22	1:200,000	2	
Jan. 27	1:200,000	2.5	
Feb. 1	1:200,000	3	
Feb. 6	1:100,000	1	
Feb. 11	1:100,000	2	
Feb. 16	1:100,000	2.5	
Feb. 21	1:100,000	3	
Feb. 26	1:100,000	4	
Mar. 3	1:100,000	5	
Mar. 8	1:100,000	6	
Mar. 13	1:100,000	7	
Mar. 18	1:100,000	8	
Mar. 23	1:100,000	9	
Mar. 28	1:100,000	10	
Apr. 3	1:10,000	2	Very slight local reaction.
Apr. 9	1:10,000	2.5	
Apr. 14	1:10,000	3	
Apr. 19	1:10,000	4	
Apr. 24	1:10,000	5	
Apr. 29	1:10,000	6	
May 4	1:10,000	7	
May 9	1:10,000	8	
May 14	1:10,000	9	
May 19	1:10,000	10	
May 24	1:1,000	1	Injection given in the office, five minutes' walk from home. Just before reaching home, patient experienced some constriction in the chest, respiration became more difficult, pallor, cough and fatigue were quite pronounced. Completely recovered in three hours. Normal the following day.
May 29	1:1,000	0.5	At home, slight reaction.
June 3	1:1,000	0.5	
June 8	1:1,000	1	Slight itching of the eyes.
June 15	1:1,000	0.5	
June 22	1:1,000	0.75	Reaction in 20 minutes. Relieved in 4 minutes by adrenalin 1 c.c. 1:1,000 and 4 c.c. sterile water.
June 29	1:5,000	2	
July 5	1:5,000	3	Slight reaction, relieved with adrenalin.
July 10	1:5,000	2	Slight reaction.
July 15	1:10,000	2	
July 20	1:10,000	2	
July 27	1:10,000	4	
Aug. 1	1:10,000	2	
Aug. 6	1:10,000	2	
Aug. 11	1:10,000	2	
Aug. 16	1:10,000	2	
Aug. 26	1:10,000	2	
Sept. 2	1:10,000	1	Slight asthma; dose cut.
Sept. 8	1:10,000	2	
Sept. 13	1:10,000	1	Dose cut account of slight asthma at time of visit.
Sept. 18	1:10,000	1.5	Reaction 6 hours later.

and has been able to exercise on a trapeze recently, whereas the mere suggestion of such exercise before her treatment would have seemed ridiculous."

In Table II, it may be seen that the local and systemic reactions were frequently encountered well along in the series of treatments. A dilution as great as 1:10,000 was necessary to avoid systemic reactions. This again illustrates the potency of this particular allergen.

A letter from the patient since returning to her school, and work in the drafting room states, "I have been working in the drafting room steadily since I returned and have had no serious attack of asthma."

TABLE II

PATIENT D. C. (AUTHOR'S CASE)

DATE	FISH GLUE EXT. DILUTION	SUBCUTANEOUS INJECTIONS (MINIMS)	REACTIONS
Apr. 18, 1930	1:100,000	2	Patient always showed a local wheal at site of injection of at least 2 mm. in diameter.
Apr. 21	1:100,000	3.5	
Apr. 25	1:100,000	4	
Apr. 29	1:100,000	5	
May 1	1:100,000	6	
May 5	1:100,000	7	
May 8	1:100,000	8	Local wheal 12 mm. in diameter. Also slight asthmatic attack, relieved by gr. ⅝ ephedrine hydrochloride.
May 12	1:100,000	5	
May 17	1:100,000	6.5	
May 20	1:100,000	7.5	
May 23	1:100,000	8	Cutaneous test with new bottle of 1:100,000 gave 2 mm. white wheal.
May 26	1:100,000	9	
May 29	1:100,000	10	
June 5	1:100,000	10	
June 8	1:20,000	1	Cutaneous tests: 1:100,000 gave 0. 1:20,000 gave 1 mm. white wheal. 1:10,000 gave 10 mm. white wheal.
June 12	1:20,000	2	2 mm. white wheal.
June 17	1:10,000	1	2 mm. white wheal.
June 24	1:10,000	1	Cutaneous tests: 1:80,000 gave 2 mm. wheal. 1:40,000 gave 10 × 5 mm. wheal. 1:20,000 gave 12 × 6 mm. wheal. 1:10,000 gave 15 × 7 mm. wheal.
During the summer the patient, on vacation in the West, received bi-weekly injections. We do not have the record of these but during this time she had one severe attack of asthma following an injection of some dilution less than 1:10,000. The attack which lasted some two hours simulated that experienced at the original test.			
Sept. 11	1:100,000	2	No reaction.
Sept. 15	1:100,000	3	No reaction.
Sept. 20	1:100,000	4	No reaction.
Sept. 30	1:100,000	4	No reaction.
Patient returned to her school.			

The clinical improvement has been much more pronounced than has any change in local or general reaction to injection of the antigen. The same thing was true in the case described in Table I.

Grutz[1] in the case of an eighteen-year-old girl sensitive to fish protein, reports the production of a severe anaphylactic reaction by a subcutaneous injection of a watery solution of fish protein. After the patient had recovered from this reaction, the sensitivity was markedly diminished.

PROPERTIES AND USES OF FISH GLUE

In the references in the literature, with the exception of a very few sources, among which are two of the above cases, the term "glue" is applied in a generic sense and no distinction is made regarding the content of the special product used. In a condition consequent to a specific protein reaction a more exact knowledge of the protein responsible is desirable, both for avoidance and for desensitization therapy. The following is a brief summary of some of the more important facts concerning glue.[6] It becomes evident that there are a number of types of glue with a considerable variation of its constituents.

In brief, glue as well as edible gelatin is obtained from animal skins, tendons, and ossein (decalcified bone) which, after treatment with saturated solution of lime, are then hydrolyzed at moderate temperatures, 70° C. to 80° C. Technical gelatin is a high grade glue, non-edible, used in certain manufacturing processes, such as photography. Next come the commercial glues used for their adhesive properties and in which little concern is paid to chemical purity. They are made from the waste products of many animals. In this category is fish glue, which is prepared from the waste products of the cod, haddock, cusk, hake, and pollock. The head, skin and trimmings are all used but best quality fish glue is made from the skins of the cod and cusk. Small amounts of some preservative, such as phenol, cresol, and boric acid are usually present as well as some essential oil to mask the odor. Fish glue has been the most important and abundant of the liquid glues.

The uses of fish glue are extensive. Among these are the making of half-tone plates and, to some extent, the production of zinc plates for photo-engraving work. Fish glues are used where flexible adhesives are required, as in book binding, in labels, stamps, and court plaster. Fish glues are much in demand for small repair jobs where liquid glue forms strong adhesive power and immediate availability is an important factor. Large quantities of fish head glue are used for sizing, box making, and cabinet work.

The cases in which definite information is given, so far indicate that of all glue products only those in which fish protein is present are found to be responsible for allergic manifestations. In none of the cases were the animal proteins outside of fish found to cause reactions

except in the one case in which horse serum was an active antigen. Without further work, such a limitation of glue sensitivity to fish protein alone would be unjustifiable, but it is strongly indicated that this is the sole cause. It is to be hoped that glue sensitivity in the future may be traced to its specific antigen, whether of fish or other origin.

EXPERIMENTAL OBSERVATIONS

Passive transfer was produced by us in four subjects. The patient's serum was passed through a Berkfeld filter and preserved in a sterile container in an ice box. About three months later, two minims of the undiluted serum were injected intradermally into the skin of the arm of a normal subject. One such injection was made in each subject. After variable periods, these sensitized areas were tested by the scratch method for different substances as noted in Table III. The reactions obtained are described there. In all instances of reaction, the resulting wheal was round and, though perfectly definite in its development, lacked the pseudopodia usually present in a positive diagnostic test on allergic patients. It seemed to be about the same size in each case and this fact suggests that the responsible agent present in sensitizing serum was fairly rapidly absorbed and fixed by the cells in limited area surrounding the original injection.

TABLE III

REACTIONS OBTAINED ON LOCAL AREAS PASSIVELY SENSITIZED WITH SERUM FROM GLUE-SENSITIVE PATIENT, D. C.

SUBJECT	ELAPSED TIME AFTER SENSITIZATION	SCRATCH TEST WITH:	RESULT
1	24 hours	Dennison glue	Reaction which reached height in one-half hour and lasted about 2 hours. Wheal approximately 1 cm. across and 5 cm. flare. Itching present.
	7 days	LePage glue	Almost exact duplicate of above except wheal slightly larger and duration was 2½ hours.
	8 days	Dennison glue	No reaction.
	9 days	Dennison glue	No reaction.
	14 days	Dennison glue	No reaction.
2	48 hours	Dennison glue	Reaction almost exactly like the first of subject 1. Wheal 9 mm.
3	4 days	Codfish protein	Duplicate of first reaction, subject 1.
4	6 days	Dennison sticker applied to arm	Duplicate of first reaction, subject 1. Wheal 1.2 cm.
	14 days	Dennison sticker	Duplicate of first reaction, subject 1.

It will be noted that the reaction so far as we have tested it, seems to be specific. There was no reaction to edible gelatin. There was no reaction to silk. (Silk is mentioned because of the theory sometimes advanced that the reaction due to silk depends upon a glue secreted by the silkworm in the preparation of its cocoon.)

It will also be observed that on Subject 1 the ability to react disappeared after the second marked reaction obtained at the end of a week. While allowance must be made for individual variation, it will be noted that in Subject 4 the reaction was still strongly positive at the end of two weeks. This suggests that in Subject 1 there was a real exhaustion of antibody at the site tested.

CONCLUSIONS

1. A case of severe reaction to glue antigen is presented with a discussion of others found in the literature.

2. The most satisfactory treatment is removal of the offending source from the environment of the patient. When this is not feasible or the source cannot be exactly determined, treatment by injections of glue allergen may be used. Such treatment by the injection of a series of minute amounts of glue allergen seems to have given beneficial clinical results which are however by no means striking.

3. Properties of glue are discussed and the hypothesis advanced that most, if not all, so-called "glue" reactions will be found to depend on fish protein alone.

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SOME ALLERGIC FACTORS IN ESSENTIAL EPILEPSY*

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THE basic or underlying mechanism of essential epilepsy still remains undetermined. Modern methods of detecting unsuspected intracranial lesions by means of encephalography and sterioscopic x-ray films have reduced the number of so-called idiopathic cases of epilepsy. Ventriculography has demonstrated a dilatation of the subarachnoid space and ventricles, in some patients with convulsive seizures; and a condition of cortical edema, observed during exploratory decompression operations following convulsive seizures, has in a number of patients been suggested as a possible mechanical etiologic factor.

Notwithstanding, however, recent pathologic findings and anatomic observations, there still remain the large majority of patients with periodic recurring convulsive seizures—the so-called idiopathic or essential epilepsies—in whom no constant definite lesions of the brain or of any other organs of the body have been found which may account for the symptoms. The clinical syndrome known as essential (nonorganic) epilepsy is regarded by many investigators as a "symptom complex of disturbed metabolism," and not as a definite disease entity.

In view, therefore, of the indefinite etiology and undetermined pathogenesis in many cases of epilepsy, it seems worth while to consider, in the light of recent investigations, certain experimental, hereditary, and clinical factors which are found to run more or less parallel in allergy and so-called idiopathic epilepsy. The hypothesis accordingly is proposed, as suggested in 1924 by Dr. Joseph L. Miller,[1] that the periodic manifestations of essential epilepsy may be a response of the system to an allergic metabolic disturbance.

The trend today of many investigators into the mechanism of both allergy and epilepsy is to consider their clinical manifestations the response of a neurogenous background resulting from a disturbed metabolic process which it seems it may be possible to transmit by the germ plasm.

EXPERIMENTAL FACTORS

Only recently Otto,[2] of the Koch Institute, following immunogenic studies covering a period of several years, reported that in rearing mice from ricin-immune fathers and normal mothers he has produced

*Read at the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

young mice who are hypersensitive to ricin, and concludes that he is dealing with an inherited subimmunity that is brought about by specific injury to the ancestral male germ plasm; and he claims thus to show spermatic transmission of experimental allergy.

Koesler, Scloss, Curschmann[3] and others have caused sensitization in guinea pigs by injecting them with serum of allergic patients. It is most important, however, as van Leeuwen[4] points out, that the possibility of transferring allergic sensitization passively to animals depends largely upon the moment chosen for the withdrawal of the blood of the allergic patient, as well as upon the intensity of his state of sensitization.

De Besche[5] and Frugoni[6] have shown that immediately after an asthmatic attack, the patient's blood does not contain the substances which might transmit to animals or to man the susceptibility to the allergen, but after some time they seem to reappear. It seems generally recognized that Frugoni has also proved that the allergic state is transmissible in the human being; that it can be transmitted through either parent, and that the form of symptoms may differ in parent and child.

Similar characteristics are noted in epilepsy. Pagniez, Mouzon, and Turpin[7] have produced convulsions in animals by transfusion of blood from epileptic patients at the time of seizure, while no convulsions occurred when the blood of healthy persons was used.

It is recognized that brain lesions in animals and human beings, in a large percentage of cases, do not produce convulsions. Collier[8] says that "epilepsy cannot be produced in a susceptible animal by injury to the brain, but it can readily be induced by introduction of a convulsant poison, such as picrotoxin, absinthe and others, into its anatomy, or by depriving the animal of one or more of its metabolic organs, such as the thyroid or parathyroid."

Miller and Dandy[9] have shown that in cats experimental lesions of the cerebrum which do not cause epilepsy can be rendered highly epileptogenous if metabolism be disturbed by the administration of a submiminal dose of a convulsant poison, such as absinthe, which has no toxic effect at all upon a normal cat. It is said that the progeny of an absinthe epilepticized animal has been shown to have convulsions Such experiments suggest that a metabolic error may be responsible for the production of convulsions.

Van Leeuwen and Leydner[10] have checked and seem to confirm their original report of isolating a muscle-stimulating substance from the blood of patients with asthma, urticaria, migraine, and epilepsy. They could not demonstrate this substance in nonallergic controls.

In a previous report[11] I cited the experience of Boston and Henry who produced recurring convulsions in two patients who were transfused accidentally with the blood of donors who had epilepsy. On the

other hand, six months ago an epileptic patient of mine was a donor without harm to the recipient, a probable evidence that the recipient's metabolism was not potentially epileptic. In view of these experimental findings and clinical observations we may hypothecate that the patient with a brain lesion who develops recurring convulsions was made potentially epileptic by a previous hereditary or acquired allergic metabolic disturbance.

HEREDITARY FACTORS

Van Leeuwen says it is generally agreed that in at least 50 per cent of cases the disposition to become allergic is inherited. Cooke and Vander Veer[12] in their extensive studies concluded that the constitutional peculiarity which makes probable the development of hypersensitiveness is transmitted according to mendelian laws as a dominant characteristic. They also found that the form of allergy in the parent is more often different from that in the offspring than it is identical.

Davenport and Weeks[13] support the hypothesis that epilepsy is due to an absence of a protoplasmic factor that determines complete nervous development. Meyerson[14] says he "is convinced that epilepsy represents injury to germ plasm, either pre- or postnatal," and Thom[15] concludes in idiopathic epilepsy that "an unstable nervous system and not epilepsy itself is the inheritable feature."

Investigating the "Familial Distribution of the Migraine-Epilepsy Syndrome" Buchanan[16] working at the Mayo Foundation studied 46 families and found that 64 of 262 children had epilepsy or migraine, giving a mendelian ratio of 3.09 to 1. Forty-four (68 per cent) of the sixty-four children had epilepsy and twenty (31.2 per cent) had migraine. In another study he found that migraine demonstrates the segregation of the determiner in the germ plasm and represents a mendelian ratio of 3.08 to 1. These ratios for epilepsy and migraine are practically identical.

In tabulating the allergic hereditary manifestations in a study of 100 consecutive adult cases of epilepsy I[17] found among the parents and grandparents: 11 cases of epilepsy, 35 cases of asthma, 7 cases of hay fever, 14 cases of hives, 6 cases of eczema, and 66 cases of migraine. One mother and two fathers of these 100 epileptic patients had epilepsy; i.e., in only 3 per cent of the parents the same clinical syndrome as in the patient was present.

MULTIPLE ALLERGIC MANIFESTATIONS

All workers in allergy report finding multiple manifestations in from one-third to one-half or more of their patients. Rackemann[18] says he finds at least a third of those patients who have one allergic manifestation have had in the past or do have at the present, some other manifestation besides the presenting symptom. Waldbott[19] re-

ports "it is common to note that asthmatic attacks are sometimes replaced by or associated with urticaria, angioneurotic edema, and other allergic conditions" and he reports two cases in which epileptiform seizures have substituted themselves for asthmatic attacks.

In my experience it is not an uncommon observation among epileptic patients to find various allergic manifestations, if a careful and searching history is elicited. In 54 of the 100 epileptic patients cited above there was a history of various allergic symptoms: 18 were or had been subject to hives; 11 to eczema; 2 to asthma; 3 to hay fever, and 19 to migraine. These accompanying or alternating allergic symptoms in an epileptic patient may be regarded, I believe, as so-called epileptic equivalents.

Just recently Dr. L. N. Boston referred to me a thirty-six-year-old man who had severe asthmatic attacks when a boy. At his fourteenth year petit mal started and the asthma has never returned, but the petit mal has continued to recur and typical major convulsions appear at longer or shorter intervals. This patient is also subject to hives and gave positive skin tests to canary and goose feathers, cabbage, parsnips, carrots, cheese, beef, and coffee.

The above-cited studies, experimental investigations and clinical observations, point to rather definite hereditary factors in both allergy and epilepsy. While it is true that in 50 per cent or more of the cases, the form of allergy is not the same in the progeny, nevertheless if the various manifestations including periodic convulsions are considered collectively as an "allergic syndrome," the clinical group runs quite true to type and points to heredity as a very definite characteristic factor; although the identical hereditary manifestations in neither condition run true to the typical mendelian characteristics of heredity.

SKIN TESTS

The generally recognized criterion of hypersensitivity as shown with skin reaction tests in allergic individuals has been investigated in epilepsy by a number of workers, and their percentage of positive and multiple positive reactions compare quite uniformly with the percentage of positive skin test findings in conditions recognized as allergic.

Ward and Patterson[20] in skin testing 1,000 epileptic patients found that 37 per cent at the Craig Colony and 56.8 per cent of those tested at Skillman were positive to raw protein extracts, whereas a control group of 100 nonepileptic persons gave only 8 per cent positive skin tests. Wallis, Nicol, and Craig[21] found 46 of 122 epileptic patients reacted positively to skin tests, while only 4 of 100 nonepileptic persons gave positive tests.

Tinel and Santanoise[22] report the very interesting fact of having shown the existence of alternating periods of sensitivity and immunity in their epileptic patients. This fact may help account for my previ-

ously reported[23] unsatisfactory experience with skin tests to foods in epilepsy, which led me to the decision that routine skin testing in epilepsy is of little assistance, since the findings are only occasionally of value in the treatment and dieting of patients with convulsions.

BIOCHEMICAL AND PHYSIOLOGIC FACTORS

In considering the possible relation of epilepsy to allergy, it is interesting to note that the viewpoint toward allergy is gradually changing from the background of a purely immunologic (antigen-antibody) reaction to include also a biochemical conception in the allergic mechanism. The chemistry of hypersensitivity and the metabolic imbalance of the allergic person are being intensively investigated. Experimental and clinical evidence is appearing in the literature to show that various factors which influence the acid-base equilibrium of the body may be an underlying factor in allergy.

Beckman[24] a year ago submitted the hypothesis that "potential alkalosis," which he defines as "the tendency of an individual to store up too much reserve alkali during the course of normal metabolism," may be an etiologic factor of importance in the allergic make-up. He stresses that alkalosis resulting from such factors as diet, climate, intercurrent diseases, and agents which tend to increase the alkalinity of the acid-alkali balance of the system predispose a person to allergic manifestations; while acids and diets like the ketogenic and acid ash, with low carbohydrate content, by producing a ketosis with a tendency to decrease alkalinity improve or prevent allergic symptoms.

The "potential alkalosis" hypothesis thus offers additional evidence that essential epilepsy may be related to the allergic state. Methods of altering metabolism which induce a systemic ketosis by use of the ketogenic diet of Wilder,[25] by the dehydration method of Fay,[26] or by the use of acid ash foods with low carbohydrate content, augmented with strict limitation of fluid intake as proposed by McQuarrie[27] have all proved of value in controlling convulsions in children and in a certain percentage of cases of idiopathic epilepsy in adults. Shifting of the acid-base equilibrium toward the acid side seems to be a factor in helping to control the convulsions in epilepsy.

With the trend in allergy to investigate the possible biochemical mechanism which underlies potential hypersensitivity, it seems only logical that the ketogenic diet, which helps to control epileptic convulsions by inducing ketosis, might be of value in allergic conditions. Within the past year Peshkin and Fineman[28] have reported encouraging results from the use of the ketogenic diet in 15 children with chronic asthma who were refractory to other modern forms of treatment; while Schnabel,[29] Barborka,[30] and others have reported on the value of the ketogenic diet in migraine.

The response of the organism to the ketogenic diet with relief of

the symptoms in asthma, migraine, and epilepsy, is offered as evidence that allergic phenomena can be influenced by conditions within the body, which may possibly be independent of an antigen-antibody reaction. Humoral disequilibrium undoubtedly is a factor in changing the metabolic susceptibility of the organism and is probably as necessary an accompanying factor in the production of hypersensitivity as are the introduction of external irritants.

Recently attention has been called by Beckman, Talbot, Trumper, and others to the report that Joslin found no case that could be definitely diagnosed as epilepsy among over 5,000 true diabetic patients. With this interesting fact pointed out, I have reviewed a series of 805 cases of epilepsy in private practice and found that none showed the presence of urinary glycosuria. Swern,[31] a month ago, reported that among 4,000 cases of clinical allergy there were only 6 cases of diabetes. Since diabetes produces an acidosis with dehydration, such surveys are significant, in the light of the "alkalosis hypothesis" in allergy and the results obtained with the ketogenic diet, and dehydration in epilepsy.

According to Trumper[32] one gram of carbohydrate holds three grams of water in the tissues while one gram of fat holds only one-tenth of a gram of water in the system. It is possible therefore that the ketogenic diet is not dependent on ketosis per se but probably, as pointed out by McQuarrie, its value is largely the result of the low level of the carbohydrate metabolism of the diet which tends to reduce the intra- and extracellular water-content of the body. This possibility is of interest in view of Fay's hypothesis that the predisposing factor in epileptic seizures is "a supracortical edema precipitated by circulatory disturbances, incident to cerebral anemia and anoxemia." All hydration states of the brain, however, are not associated with convulsions, and it has not been definitely agreed that the hydration state is not an effect rather than the cause of convulsions. Furthermore, the relation of the systemic water balance to the acid-base equilibrium of the body is not clearly understood.

That anaphylactic phenomena are influenced by the sympathetic nervous system as evidenced by smooth muscle contraction of vessels and glandular secretions, is recognized by most investigators. Angiospasm is regarded as a characteristic vascular phenomenon in allergy, and Olkan[33] who has studied the problem of epilepsy from the physiologic point of view concludes that "epilepsy is attributable to a vasomotor disturbance of the capillaries." All vasomotor disturbances in the brain, however, do not result in convulsions, and it is probable that the potential allergic background in the epileptic patient makes it possible for the vasomotor disturbance to act as an exciting cause, just as brain lesions in animals as a rule do not cause convulsions unless the animal has been previously "epileptoginized" by a poison. Such find-

ings are suggestive evidence that an altered metabolism is necessary to make the patient susceptible to sensitizing toxins or allergens arising either from within the body or introduced from without.

Whether, then, the immediate cause of the epileptic convulsion is as Bossard and others consider, a mechanism similar to "anaphylactic shock," as evidenced by the leucopenia and marked fall in blood pressure which immediately precede a seizure; or is due to a "vasomotor disturbance of the cerebral capillaries"; or is concerned fundamentally with a disturbance of the systemic water balance, it nevertheless is evident that the most recent biochemical studies in epilepsy tend to run parallel to present-day trends in investigating the mechanism of allergy, and are intimately concerned with the acid-base equilibrium and water-balance factors of metabolism. It is reasonable, therefore, to presuppose that in the etiology of epilepsy and allergy there may possibly be an associated similar metabolic error, and future progress in investigating the mechanism of the allergic state must depend, it would seem, more largely upon a study of biochemical alterations and physiologic disturbances that permit of a metabolic imbalance which makes the soil, as it were, suitable for the development of hypersensitivity.

CLINICAL FACTORS

Besides the hereditary, experimental, and metabolic factors there is also considerable clinical evidence which points to the probability that many of the convulsions in so-called idiopathic epilepsy develop from an allergic background. Among the foremost clinical factors which argue in favor of an allergic metabolic dyscrasia, as a cause for essential epilepsy, is periodicity. Periodicity and the paroxysmal nature of the attack are just about as characteristic of asthma, urticaria, and migraine as they are of epilepsy. In some epileptic patients convulsive seizures occur only at night or only in the daytime, or weekly, or monthly, or there will be a series of attacks at long intervals, and we are unable by any ordinary means, as a rule, to produce attacks during the long interparoxysmal periods. Such periodicity in epilepsy is certainly more reasonably explained on the grounds of an allergic metabolic disturbance—now present, now absent—than on any hypothesis of disease, irritability, or functional derangement of the brain.

The epileptic attack, Collier[8] says, is probably the result of some error of metabolism allowing the development of a toxin, which as Hortenberg suggests, causes "paroxysmal inhibition of cerebral function." This paroxysmal tendency is characteristic of the metabolic disturbance in various allergic states. The bronchospasm (smooth muscle contraction) which suddenly disturbs normal respiratory function is well recognized in the asthmatic attack.

Other clinical characteristics common to epilepsy and allergy which

have been pointed out from time to time are that the attacks start abruptly, that one attack tends to predispose to another, and that the attack per se is rarely fatal. It has for a long time been noted that intercurrent diseases, at least temporarily, benefit allergic states and in epilepsy lengthen the interval and in some instances entirely relieve the patient of convulsive seizures. The pregnant woman who has no attacks of asthma, migraine, or epilepsy during gestation probably has her faulty metabolism corrected by the presence of the fetus, which may possibly act as a nonspecific anti-allergic desensitizer.

Hyperventilation in certain persons has long been clinically known to bring on temporary symptoms of tetany, and Collier[8] reports that in recent clinical research, hyperventilation has promptly produced a convulsion in over 40 per cent of the epileptic patients tested. The factor which produces this effect in epilepsy is attributed to the state of alkalosis which results from a washing out of the carbon dioxide from the blood and tissues through the lungs.

Trumper,[32] quoting Haldane, says that anoxemia is accompanied by alkalosis and experimental anoxemia has been shown to augment epileptic seizures. On the other hand, experimentally and clinically the rebreathing of carbon dioxide in increased concentration has been found to favorably influence epileptic seizures. I have a patient at the present time who, when his aura (an auditory sensation) appears, can prevent a convulsion by holding his mouth closed and pinching his nose for from one and one-half to two minutes, thus retaining, as it were, his own carbon dioxide. From these findings it is evident that so simple a disturbance of metabolism as alteration of the oxygen, carbon dioxide, and buffer salt relation in the blood may bring on an epileptic seizure.

THERAPEUTIC FACTORS

While some of the clinical characteristics common to epilepsy and allergy may be regarded as more or less presumptive, there is considerable therapeutic evidence to support the hypothesis that epilepsy is related to allergy. Epinephrin usually relieves the acute paroxysm of asthma but if it fails, morphine almost surely will; the same is true, I have experienced, in serial epileptic convulsions.

The results obtained with the ketogenic diet in epilepsy, migraine, and asthma, and also by limitation of fluids in epilepsy, help to control or lessen the frequency of the acute symptoms in many cases, especially in children. These results are attributed by most investigators to a lessening of alkalosis. Keith,[34] however, a few months ago reported in experimental convulsions, produced by Thujone (a constituent of the volatile oil of absinthe), that rapid dehydration reduces the susceptibility of rabbits to experimental convulsions. He found that acetone and diacetone alcohol also reduce the susceptibility of the ani-

mal to experimental convulsions, but that these drugs do not cause dehydration of the brain tissue. He is studying the action of ketone substances and intimates that their action is probably an anesthetic one, as originally suggested by Wilder.

The therapy most needed, however, in allergy and epilepsy is a basic one that can be used interparoxysmally and which will tend more permanently to restore the metabolic imbalance. For this purpose the effects of nonspecific desensitization must be given consideration. The use of tuberculin, peptone, typhoid vaccine, milk, and other agents have proved of undoubted value in epilepsy as well as in asthma, urticaria, migraine, and other forms of allergy, as reported by various and many observers.

Twenty years ago I began the empiric use of crotalin (a solution of the dried venom of the American rattlesnake, Crotalus horridus) and have reported[26, 35] on its use from time to time in the treatment of epilepsy, asthma, and migraine. In treating over 800 cases of epilepsy in private practice since 1909, I have found that a solution of crotalin given intramuscularly in doses varying from $\frac{1}{400}$ to $\frac{1}{50}$ of a grain, at intervals of from seven to twenty-one days, has produced clinically some very satisfactory results. Among my case records are reports of patients who have been free from convulsions for from five to fifteen years. A number of other clinicians, including Calmette,[37] Fackenheim[38] and FitzSimons,[39] have reported encouraging results with the use of snake venom in the treatment of epilepsy.

Various workers, including Weir Mitchell (1860-1890), Mitchell and Reichart (1883), Flexner and Noguchi (1903), Newman (1904), and Rodgers (1905), have investigated the chemistry and certain phases of the physiologic action of venoms in animals. During the past year, however, a most comprehensive and carefully controlled investigation into "The Physiologic Action of Crotalin" has been reported in a series of ten papers by Essex and Markowitz [40, 41, 42] and their associates from the Mayo Foundation. Their findings help undoubtedly to explain many of the therapeutic results clinically reported.[43] These investigators have pointed out "the striking ability of crotalin to influence the migration of water through cell membranes." They have shown that "the albumin content of crotalin reduces blood pressure by peripheral vasodilatation, notwithstanding its marked ability to increase the viscosity of the blood by a swelling of the erythrocytes." Their experiments further indicate that the degree of immunity acquired by dogs after the injection of a series of graduated doses of venom can be gauged by the blood pressure. When the results of these experimental findings are more fully correlated and can be applied clinically with physiologic regulation of dosage, I am convinced, in the light of present-day biochemical and physiologic factors found

operative in allergy, that crotalin as an aid in restoring allergic imbalance will be more widely used.

As an adjuvant to crotalin therapy in epilepsy and allergy the feeding which has given the most satisfactory service in my hands during the past year has been a modified ketogenic diet with a low carbohydrate content embodying a preponderance of acid ash foods in a ratio of three or two parts of acid ash, to one of alkali ash, as suggested by McQuarrie.[27] A liberal use of olive oil and dilute hydrochloric acid after meals has also been prescribed. Cannavo[44] in a clinical study of "Intermediate Metabolism of Fats" reports that all acids of the aliphatic series produce acidosis, but only those that have an odd number of carbon atoms are intensely ketogenic. Olive oil fulfills this requisite. Fleuret[45] reports that the addition of hydrochloric acid to the food diminishes the excretion of ketone bodies, but there is no relation between the excretion and the total acidity or alkalinity of the urine. This diet and therapy have seemed to be enhanced in some cases by limiting the fluid intake (dehydration), as recommended by Fay. In most adults, however, the necessity of continuing the strict limitation of fluids over long periods of time becomes almost a torture and often is entirely impracticable.

SUMMARY

1. With the mechanism of so-called "idiopathic epilepsy" still indefinite, certain experimental, hereditary, biochemical, clinical, and therapeutic factors, which run more or less parallel in allergy and essential (nonorganic) epilepsy, are considered in support of the hypothesis that periodic convulsive manifestations may be a response of the system to an allergic metabolic disturbance.

2. Experimental evidence to show spermatic transmission of allergy and instances of passive transfer of the allergic state and of epilepsy, from human beings to animals and from person to person are cited. It is postulated that brain lesions in animals and human beings do not, in most instances, produce convulsions unless the system has been previously made potentially epileptic by a convulsant poison or allergen.

3. It is pointed out that hereditary factors are more or less similar in allergy and epilepsy, and if their various manifestations are grouped as an allergic syndrome, they run quite true to the typical mendelian type. When convulsive seizures are accompanied by or alternate with attacks of migraine, asthma, urticaria, allergic dermatitis, etc., the allergic symptoms may be considered as "epileptic equivalents."

4. The percentage of positive skin test reactions for hypersensitivity compares very uniformly in allergy and epilepsy.

5. Biochemical investigations of the allergic state have certain factors in common with recent findings in epilepsy. Evidence is cited which tends to show that allergic phenomena may be influenced by

metabolic conditions which may possibly be independent of an antigen-antibody reaction. The "potential alkalosis" hypothesis applies to both allergy and epilepsy, and diets and other means of producing ketosis are found to relieve asthma and migraine as well as to control epileptic seizures. The basic mechanism of diabetes, with a decrease of alkalinity, appears to be antagonistic to that of epilepsy and asthma, in which conditions an increase of alkalinity is present. Evidence is accumulating that the underlying metabolic error in allergy and epilepsy is intimately concerned with a disturbance of the acid-base equilibrium and water balance factors of the system.

6. Clinical factors common to allergy and epilepsy include paroxysmal periodicity, the fact that attacks usually start abruptly and one attack predisposes to another, and that symptoms are at times relieved by an intercurrent condition. Hyperventilation and anoxemia which cause an alkalosis augment epileptic attacks, while rebreathing of carbon dioxide in increased concentration by decreasing alkalinity favorably influences convulsive seizures.

7. Therapeutic evidence that epilepsy may be related to allergy includes:

(a) The observation that when epinephrin does not relieve the acute attack of asthma or serial convulsive seizures, morphine usually will.

(b) The interparoxysmal use of nonspecific desensitization therapy has been found of value in allergic conditions and also in epilepsy.

(c) The intramuscular injection of crotalin has been of value in epilepsy, migraine, and asthma. Its influence on the disturbed metabolism in allergy is probably to some extent explained by the recent reports on the physiologic action of crotalin by Essex and Markowitz, who find in animals that "crotalin reduces blood pressure by peripheral vasodilatation" and that it has "a striking ability to influence the migration of water through cell membranes."

8. As adjuvants to the intramuscular injection of crotalin in epilepsy and allergy a modified ketogenic diet with liberal use of olive oil, for its intensely ketogenic qualities, and dilute hydrochloric acid after meals, for its influence in diminishing the excretion of ketone bodies, have been found of clinical value. This diet and therapy have seemed to be enhanced, in some cases, by limiting of the fluid intake.

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(For discussion, see page 83.)

ALLERGY IN DUODENAL ULCER: INCIDENCE AND SIGNIFICANCE OF FOOD HYPERSENSITIVENESS AS OBSERVED IN 32 PATIENTS*

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THE thought that allergy might be a factor in the etiology of duodenal ulcer was suggested by the following case:

CASE REPORT

M. M., a man aged thirty-five years, gave a history of digestive disturbances since childhood. At the age of twenty-eight years his symptoms grew worse and terminated in the perforation of an ulcer. At operation a duodenal ulcer was cauterized and oversewn, and a posterior gastrojejunostomy done. After the operation the patient adhered to no special diet and followed no treatment. One year later, at the age of twenty-nine years, he suffered the symptoms of a second perforation. At operation a perforated jejunal ulcer was cauterized and oversewn. At this time he first came under our observation. On alkali medication and a bland diet he felt fairly well for a number of years. He then became careless and began at times to eat foods which were known to cause abdominal discomfort and indigestion. Two years ago, at the age of thirty-three, there was again a seizure of severe upper abdominal pain, but this time without evidence of peritonitis. Nevertheless, because of past performances, an exploratory laparotomy was done, and there was found a "kissing" ulcer which had perforated from one loop of jejunum into another, automatically performing a jejunojejunostomy. Since then the patient has been practically symptom-free and has adhered strictly to a diet free from all foods which, by experience, were known to cause discomfort, as well as those foods to which his skin reacted.

Because of the definite relation of the patient's symptoms to certain foods, a personal history of urticaria and a family history of food eczema in his sister and his son, skin tests were performed. They showed weak reactions to a number of foods, only some of which, according to the patient, provoked symptoms whenever eaten. On the other hand, certain foods which invariably caused symptoms failed to give positive skin reactions. For instance, apple, cantaloupe, lettuce, onion, and watermelon all gave positive skin reactions and all

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produced symptoms, while cocoa, crab, and peach reacted but failed to produce symptoms when eaten. Beef, buckwheat, cabbage, corn, oat, milk, and rice always produced symptoms but gave negative skin tests. The apparent hypersensitivity to milk made it difficult to carry out a Sippy type of treatment. A rice water mixture, as described by Schnabel,[1] was substituted for milk but had to be abandoned because the eating of rice caused pain. Finally, a barley water mixture was tried and proved successful. On the basis of these data it seemed justifiable to suspect an allergic factor in the etiology of this patient's ulcers.

A survey of the literature shows that the possibility of allergy as a cause of peptic ulcer has variously been considered. The evidence at hand is, however, extremely slight. From the experimental standpoint, Demel[2] in 1923 suggested, because of the similarity of the vascular changes, that some ulcers might be manifestations of local anaphylaxis. He suggested that the lesion might be either in the nature of an Arthus phenomenon or perhaps similar in its beginnings to an urticarial wheal. Ivy and Shapiro[3] in 1925 were able to produce in rabbits, lesions resembling peptic ulcer by injecting into the gastric mucosa a foreign serum to which the animals had previously been sensitized. Alessio[4] in 1928 and Vallone[5] in 1929 made similar experiments with somewhat divergent results. The clinical evidence is even more meager and is limited to the statement in general articles that anaphylaxis or allergy may possibly be a factor in the etiology of ulcer (Ivy,[6] Levine,[7] Lipschutz,[8] Wellbrock,[9] Ivy and Fauley[10]), and to a few isolated case reports in which such an etiology was suspected (Carr,[11] Sterling,[12] Rowe,[13] and Snorf[14]).

It, therefore, seemed desirable to study a series of unselected ulcer cases from this standpoint. Observations were made on 32 patients: thirty from the Gastro-enterology Section of the Medical Clinic and from the wards of the Hospital of the University of Pennsylvania, and on two private patients of Dr. Simon S. Leopold. The patients were all adults ranging in age from twenty-three to sixty-three years. There were twenty-eight males and four females. In 20 instances there was operative proof of the diagnosis of duodenal ulcer, and in the remaining 12 there was unequivocal roentgen-ray and clinical evidence of the disease. In each instance a careful history from the allergic standpoint was taken. Laboratory studies, including a differential blood count, were made. Skin tests for foods eaten were performed and, whenever possible, a clinical check on the results was attempted.

Although the number of patients studied is entirely too small to afford any absolute significance to percentage figures, nevertheless the incidence of recognized allergic disease in the patient or his family is sufficiently high to attract attention.

In Table I are summarized the data on the incidence of allergic conditions in the 32 patients and their families. A 40 per cent incidence of personal allergy is certainly much higher than the average. In spite of the fact that men are usually poorly informed concerning a family history of allergy—and 28 of our patients were males—more than one-fourth gave a positive family history. In two cases, both males, there was a family history of duodenal ulcer in a sister, proved in one instance at operation, and in the other by roentgen-ray examination.

TABLE I

INCIDENCE OF PERSONAL AND FAMILIAL ALLERGY

Total number of patients		32
Patients with familial allergy		9 (28%)
Patients with personal allergy		14 (40%)
Patients with either familial or personal allergy		16 (50%)
ALLERGIC CONDITION	PERSONAL HISTORY	FAMILIAL HISTORY
Asthma	2 cases	5 cases
Hay fever	4 cases	3 cases
Urticaria	7 cases	3 cases
Eczema	1 case	3 cases
Migraine	2 cases	1 case
Familial history of proved ulcer		2 cases

The presence of eosinophilia may be considered suggestive of an allergic state, but its absence does not rule out allergy. A true eosinophilia was noted in only two patients with figures of 8 and 6 per cent, respectively; the former gave a history of asthma, but the latter had no personal allergy. Two patients showed 4 per cent of eosinophiles, and five others gave a count of 3 per cent. Of the latter, one patient had asthma, hay fever, and eczema, and another had hay fever and eczema.

TABLE II

SKIN TEST RESULTS (CUTANEOUS METHOD)

	CASES WITH POSITIVE REACTIONS		CASES WITH ONLY DOUBTFUL REACTIONS		CASES WITH ONLY NEGATIVE REACTIONS	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
To foods	19	60	8	25	5	15
To inhalants	6	23	--	--	20	77

Skin tests were performed by the cutaneous method to the foods eaten by each patient, and in most patients also to the commoner inhalants. A reaction of one centimeter or more in diameter was recorded as positive, between one half and one centimeter as questionable, and less than half a centimeter as negative. As is commonly the case with food reactions done by the cutaneous method, the positive reactions obtained in these patients were by no means so marked as pollen reactions in hay fever cases, or even as

food reactions in children. Although 60 per cent of the patients gave one or more definitely positive reactions, these reactions often did not check with the clinical history. Reacting foods in some patients failed to cause symptoms, and in others, foods which did produce symptoms failed to react.

The foods to which definite positive reactions were obtained and the number of reactions to each are listed in Table III. Foods which gave only questionable reactions are not listed.

TABLE III

FOOD	NO. RE-ACTIONS	FOOD	NO. OF RE-ACTIONS	FOOD	NO. OF RE-ACTIONS
Clam	4	Buckwheat	1	Mackerel	1
Vanilla	4	Carrot	1	Onion	1
Cantaloupe	3	Celery	1	Pea	1
Cocoa	3	Cheese	1	Peach	1
Eggplant	3	Cherry	1	Potato	1
Cabbage	2	Cocoanut	1	Pork	1
Coffee	2	Corn	1	Prune	1
Oat	2	Duck	1	Radish	1
Parsley	2	Egg	1	Rhubarb	1
Pepper	2	Fig	1	Rye	1
Raisin	2	Ginger	1	Squab	1
Tuna fish	2	Grape	1	String bean	1
Banana	1	Hazelnut	1	Tea	1
Beet	1	Lentil	1	Watermelon	1
Blueberry	1	Lettuce	1	Wheat	1
Brussels sprouts	1				

It was our hope to put each patient to a clinical test by observations made during two periods: The first period on a diet from which foods that reacted positively or doubtfully had been excluded, and the second, one in which these foods were used freely. Unfortunately, we were able to carry out this program in only a few cases. The patients were not under our direct supervision, so that it was difficult completely to control conditions. It was not hard to have the patients put on a diet from which the reacting foods were omitted, or even to feed the patients for a time these foods in large amounts, but we often failed to keep the patient from receiving other forms of treatment so that it became impossible to interpret results.

The results of the clinical tests in the patients so studied are presented and analyzed in the succeeding paragraphs. There was a definite history, in nine patients, that the eating of certain foods always produced symptoms (particularly epigastric pain and discomfort). In four of these the suspected foods gave positive skin reactions, in four others they gave negative reactions, and in the ninth case, they were not tested. In thirteen patients no history of such a food relation to symptoms could be elicited. There are no data on this point in the records of the remaining ten patients.

Six patients, for a period of two weeks, were placed on a diet from which reacting foods had been eliminated. They received no other treatment during this time. All six were symptom-free. Similarly, sixteen patients were observed while on a diet in which reacting foods were included daily. In five patients there resulted definite epigastric pain and discomfort. Eleven patients were symptom-free on this diet.

There are two points to which we wish at this time to call attention, although we fully realize that our scanty evidence is scarcely more than suggestive. In the first place, of the nine patients who seemed to show a relation between the eating of specific foods and the occurrence of abdominal symptoms, three also gave a history of personal allergy, had positive skin tests, were relieved of symptoms on a nonreactor diet, and suffered a recurrence or aggravation of symptoms when on a reactor diet. In other words, a history of a relation between the taking of specific foods and the occurrence of symptoms may be considered suggestive of possible food hypersensitiveness. The other point is this: Of five unoperated patients who were placed on a diet of foods to which they reacted, three suffered symptoms. Of eleven patients who had had a gastroenterostomy performed and who were so dieted, only two suffered symptoms, whereas the other nine were able to eat with impunity all the reacting foods, a number of which had always provoked distress before operation.

Of particular interest is a group of six cases in which there had been a recurrence of ulcer after operation. In four of these the diagnosis of recurrent ulcer was based on history and on roentgen-ray findings. In the other two, ulcer was found at operation, including the first patient described, who had three perforations. Three of the six gave a personal history of allergy (migraine two, urticaria one). In three cases there was a family history of allergy (migraine one, urticaria one, eczema one). Four of the six gave either a personal or a family history of allergy, and in two both were present. None showed eosinophilia. In three of these cases there were definitely positive skin tests, and the other three gave weak reactions. Two of the six each showed all of these points: personal allergy, familial allergy, a definite relation of symptoms to the ingestion of certain foods, and symptoms of abdominal distress when fed the reacting foods, both after operation as well as before. Only one could eat the reacting foods without ill effect.

The etiology of duodenal ulcer is largely still obscure. Possible factors involved in the production of ulcers are considered at length in general discussions of the subject, but in the study of the individual case they receive scant attention. This is largely due to the futility of our efforts to find in any given case a real cause, except perhaps focal infection, or to our inability to eliminate or set it aside, as, for

example, a so-called constitutional ulcer habitus or a disturbed autonomic nervous system. Our measures of treatment, therefore, resolve themselves almost wholly into attempts to control abnormal physiologic processes (hyperacidity and pylorospasm) and to relieve the effects of organic change (obstruction, bleeding, and perforation).

The evidence which we have here presented is meager and based upon a wholly inadequate number of cases to warrant any fine-drawn, statistical conclusions. We are convinced, however, that it is strong presumptive evidence that duodenal ulcer can occasionally arise solely on a basis of food hypersensitiveness and, furthermore, that in some cases it may be one of the several associated factors. How frequently allergy is an etiologic factor is not known; probably in only a small minority of all cases, or else ulcer would not have such a decided difference of incidence in the two sexes. We do believe, however, that it is a factor in an appreciable minority and not just in a rare or occasional instance. Especially in those cases in which ulcer recurs, even after radical surgical procedures, one should be on the alert to discover a possible food hypersensitiveness.

In attempting to discover such a food allergy, we wish to emphasize that skin testing alone, whether by cutaneous or intracutaneous methods, is not sufficient. Symptom-producing foods may give consistently negative skin reactions. It becomes necessary, therefore, to question the patient carefully concerning the relation of symptoms to the eating of specific foods. With this information, in addition to the skin test findings, it becomes possible to prescribe elimination diets to good advantage. This is a method which many patients have learned to use through hard experience. Their attempts in this direction, however, are mostly doomed to failure through the patient's own inexpertness. It is here that the physician can be of greatest assistance.

SUMMARY

Evidence has been presented which tends to show that food hypersensitiveness may be an etiologic factor in a small but appreciable percentage of cases of duodenal ulcer. Especially in those cases in which ulcer recurs after operation should an allergic factor be suspected. Its recognition in any case puts the treatment of that patient upon the sound and successful basis of removing a cause.

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METEOROLOGIC ASPECTS OF THE NATIONAL RAGWEED POLLEN PROBLEM*

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THE immense influence of meteorologic phenomena on the health, happiness, and prosperity of the human race is justification enough for the popularity of "weather" as a topic of common interest. The study of meteorology is not only interesting but often highly profitable. It is well worth while for the merchant, the butcher, and the baker, as well as the stock broker and the farmer to study the weather reports, and it is not less important for the doctor to know what is "in the air." The kind of weather prevailing on this very day (June 9) and during this week throughout the United States is of vital interest to the ragweed hay-fever victim, and consequently, to the physician called upon to pilot him over the mountain peaks of high atmospheric ragweed pollen concentration of August and September.

Our knowledge of the effect of the various atmospheric conditions upon the comfort of these sufferers is being rapidly increased.

Four years ago, Doctor Balyeat read a paper before this Society in which he enumerated and discussed the principal weather factors affecting atmospheric pollen incidence. His deductions, which are now being proved essentially correct, were based only on personal observation and the inadequate statistics furnished by three local midwestern atmospheric pollen studies, only one of which was his own work. The three studies were not even coseasonal, one having been made a year previous to the other two. These were all the data then available. To these three studies have been added during the past four years, considerably over 100 similar studies, about half of which have been so controlled as to yield unquestionably uniform statistics. The 112 atmospheric ragweed pollen studies reported or known to me at this time include figures from fifty-three cities in twenty-nine states, the District of Columbia, and four Canadian provinces. The exposures made during the past two seasons in over forty localities by the aid of the United States Weather Bureau and Canadian Meteorological Service have furnished a mine of dependable data suitable for correlation with the almost limitless meteorologic figures supplied from the same sources.

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From Biological Laboratories, Abbott Laboratories, North Chicago, Ill.

Without accurate, adequate statistics, it was impossible for Dr. Balyeat to evaluate the factors which he enumerated. Even now, we cannot be too certain of our conclusions, so it is planned to continue the work with the Weather Bureau for several seasons. We have found in atmospheric pollen research a valuable tool, but with which there are furnished no printed instructions. Untangling the threads of half a dozen highly variable and often interdependent factors is certainly no easy task.

While there are growing within the borders of the United States more than 100 species of ragweed (*Ambrosiaceae*), it is safe to say that over 90 per cent of the annual fall atmospheric load is produced by our two common species, short ragweed and giant ragweed. Both of these species are unusually vigorous annual plants and extremely adaptable. Both prefer loose rich soil, but on account of its heavier foliage, giant ragweed demands more moisture than short ragweed and is consequently much more affected by variations in rainfall. The ideal conditions for heaviest ragweed pollen production are: average summer temperature 70° to 80° F., and total spring and summer rainfall of 10″ to 25″. Ideal conditions for maximum pollen ripening and transport are: dry, sunshiny weather with occasional rains only at night, high winds, low humidity, and temperature not less than 50° F.

The present accumulation of data allows us to study these weather factors by several methods. The simplest method of study and that requiring the least information is correlation of the fluctuations of a local pollen curve during one season with, for example, fluctuations of temperature. Sometimes the percentage of positive correlation is strikingly high, and other times very disappointing. More reliable deductions can be drawn from several succeeding annual records for the same station or coseasonal records from a number of stations. Each factor must be studied alone and correlations plotted regardless of any other factor. It is also often possible to select situations where all important factors except the one being studied are equal.

Of the meteorologic phenomena influencing the annual pollen crop, rainfall is by far the most important, even more important than wind movement. Its greatest effect is preseasonal. A year is favorable or unfavorable to plant growth and maturity largely depending on the adequacy of spring and summer rainfall. The amount of precipitation has a greater daily and annual variation than wind velocity, temperature, sunshine, or any other factor. As an example of this variation, there were certain districts in the United States which received, during the summer of 1930, less than one-tenth of the rain received during the summer of 1929. The widespread drought of 1930 has served to emphasize the great importance of moisture on the development of ragweed. As would be expected, giant ragweed suffered much more than short ragweed, with the result that in many places there was al-

most no ragweed pollen in the air during the first two weeks of the usual ragweed season. Statistics seem to indicate that the amount of rainfall in July has more influence on the pollen crop than the rainfall of any other similar period during the spring and summer.

August rainfall is of special interest. A moderate amount of rain is needed throughout the month to insure ripening of pollen but after August 15 it makes considerable difference whether the rains come during the day or night. Night rains at this time are an aid to pollen maturation and only a slight hindrance to transport. Day rains during the flowering, however, especially if they occur during the forenoon, interfere greatly with pollination. In most parts of the United States there are no prolonged rainy periods during August and September, and the total effect of coseasonal rainfall is almost negligible. Humidity is much more important and will be discussed in connection with sunshine.

The study of the effect of wind on pollen incidence is made difficult by the fact that wind direction is sometimes more important than its velocity. A brisk wind during the early morning is much more important than a similar wind later in the day or at night. It is also obviously impossible to know at just what time of the twenty-four hours during which the slide has been exposed that the greatest amount of pollen has fallen. We know that, as a rule, the most of the pollen is deposited on the slide during the forenoon. In a few instances we have obtained hourly wind records and in one instance have made hourly slide exposures, but it is impracticable to carry out a national study in so much detail. It is settled, however, that wind movement, including ascending convection currents, is the principal coseasonal factor influencing pollen incidence, as it is the only distributor and because the factors influencing the ripening of pollen are not markedly variable at this time of year. In some localities wind direction is of the utmost importance, for example, where industrial conditions or natural barriers cause the source of supply to lie in a definite direction. It has been noted that New York City gets almost all its pollen from New Jersey. Chicago and Cleveland are examples of cities with natural barriers. The so-called "land and sea breezes" caused by the presence of large bodies of water, are best studied at locations such as Cleveland and Toronto or Chicago. There is a tendency for the winds to blow from a large body of water during the warm part of the night. Since prevailing winds in the Great Lake area as a whole at this season of the year are from the southwest, lake breezes at Cleveland are prevented, as a rule, until about noon and land breezes are reestablished early in the evening. The reverse is true at Toronto, situated as it is on the north side of Lake Ontario. Here, lake breezes are established earlier in the day, coming from much the same direction as the general prevailing winds. This would be expected, as lake breezes

are much more prevalent at Toronto than at Cleveland and pollen incidence is accordingly much less. I am even suspicious that a fair proportion of Toronto's pollen originates on the opposite side of the lake.

Sunshine is a factor which is more easily studied than wind movement, and ranks next to it in importance. It is all-important in the ripening and discharge of pollen. Just how much of its effect is photochemical and how much is thermal, causing dissipation of moisture and consequent lowered humidity, is a subject for further study. I am inclined to think, however, from my experience in maturing pollen in the laboratory, that the photochemical effect of sunlight is much the more important. Obviously, as with wind movement, the critical time for the effect of sunshine is the early morning hours. Given sunshine for two or three hours in the early morning, it makes very little difference about the state of the sky for the rest of the day.

The amount of sunshine determines to a large extent the temperature and relative humidity. The percentage of correlation of either of these factors with pollen incidence averages about the same and their correlation with each other is very high. Frost is seldom of any consequence. Ragweeds must not only mature pollen, but must set and ripen seeds before frost, and they are acclimated in each locality so that pollination ceases three or four weeks before killing frost. Pollination is much retarded by unseasonably cool weather, but it is hard to prove that temperature is alone responsible.

The effect of barometric pressure on pollen incidence cannot be discussed without reference to the part played by cyclonic disturbances which follow each other across the United States, in a general direction of west to east. Barometric pressure is not known to have any direct influence on plant life, but barometric changes are used in plotting the progress and predicting the movement of cyclonic disturbances. With these, the disturbances are associated in a very definite way, with striking changes in temperature, wind direction, and wind velocity, as well as precipitation. During August and September, as in all other months, centers of low barometric pressure cross our northern states every few days, as a rule. In the area south and east, the center of these low pressure areas, southwest winds are almost always present. They are usually accompanied by warm, dry weather and ascending air currents. As soon as the low pressure area has passed east of a given point, rains are likely to occur, followed by a shift of wind to the northwest, with accompanying clear, cool weather. When these cyclonic disturbances are well marked, their effect on pollen curves throughout the United States is very striking. If it happens that one of these storms coincides with the period of heaviest pollination, very high pollen counts will be found on the slides. If the apex of pollination happens to be between two storm periods, the result will likely be a "saddle" curve.

Since it is through a study of the movement of high and low pressure disturbances that short-time weather predictions are made, it is possible by the same means to predict the fluctuation of pollen distribution. Every physician engaged in the study of pollen allergy should have the local daily weather report during the pollen season. He should not only read the prediction but should learn to interpret the movement of storms, as shown on the map. If he can anticipate by even twenty-four hours the ups and downs in his patient's symptoms, both he and his patient will be the happier for it.

(For discussion, see page 93.)

A NOTE ON THE QUANTITATIVE SURVEY OF POLLEN*

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IN HAY FEVER sufferers, the clinical symptoms vary so greatly from year to year as to be difficult to understand or explain unless on a basis of seasonal variation. It is generally agreed that the amount of pollen with which a hay fever patient comes in contact determines the severity of the symptoms. Therefore, a year in which the pollen content of the air is at a minimum is designated as a "good" year symptomatically. Atmospheric counts of the pollens, correlated with weather and climatic conditions give us a reasonable explanation of the variation of the seasonal conditions and the severity of the symptoms. A check postseasonally when all of the counts for the entire season have been completed and charted shows that the symptomatology and the atmospheric pollen content run parallel. Climatic factors which influence the pollen counts and must be taken into consideration are: wind velocity, amount of rainfall, temperature range and variation, atmospheric humidity, and the relative amount of sunshine for the season.

As in former years, a quantitative pollen survey was carried out from August 16 until there was no more pollen free in the air (approximately Oct. 18, 1930). Only a record of the common offenders was kept. The survey was divided into two portions: first, the daily pollen count, counting ragweed, plantain, and goldenrod to determine a daily average; second, a survey to determine the effect of height and temperature as factors influencing clinical manifestations.

For the first part of this experiment the roof of the Germantown Hospital in Philadelphia was chosen. This is the same site which was used previously in 1928, so it offered a basis for comparison. This, in position, is equal to a six-story building and is set high on a knoll of ground commanding an uninterrupted sweep of the usual suburban fields. It represents a position in the typical residential area about Philadelphia.

TECHNIC

Two slides are coated on one side with a white vaseline in a thin even film and exposed for twenty-four hours. We have found it most advantageous to begin the time from noon one day until noon the next. The apparatus shown in Fig. 1 was designed to hold the slide.

*From the Wilmer Research Foundation in the Laboratory of the Germantown Hospital, Philadelphia, Pa.

Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

It is designed to protect the exposed slides from the direct rays of the sun, from the rain and from the large particles of dust and soot which fall on the slides and make counting difficult. It is a weather vane arrangement made of sheet tin and so constructed that the exposed slide is held in the direction of the wind. It is set on a pin and freely movable, swinging at will, thus compensating for changes in the direction of the wind.

Counting.—A low power field is used, and beginning at the edge of the slide a count is made of the number of pollen grains of the types being counted which are found in crossing the slide. The slides used averaged 24.8 mm. in width. The field is then changed and another count crosswise is made. The total count of five such crossings of the slide is the approximate number of pollen grains per cubic yard of air. In

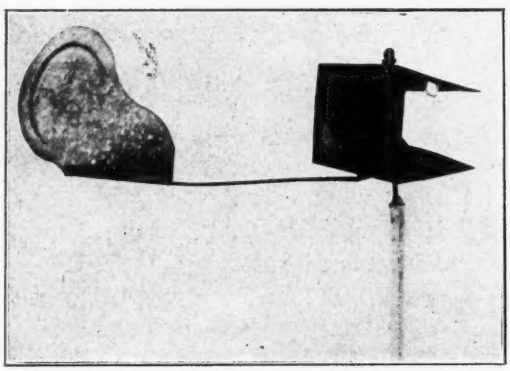

Fig. 1.

order to get a more accurate average, ten fields are used and averaged to give the number for one field, multiplying by five gives the desired number for the five fields.

Koessler and Durham[1] in a report of an air pollen survey gave a very satisfactory method for an intensive pollen survey. In 1928 Durham[2] reported a comparative analysis of nine large cities for ragweed pollen. We submitted to them our reports for the surveys done in Philadelphia for that season (1928). We find that this past season has been different from any of the previous ones. The pollen content of the air reached a peak later in the season and was a protracted one. There was a marked variation from the normal rainfall this past season as well. The year 1930, with its marked drought period and variation of the rainfall from a normal precipitation showed also a decidedly different pollen chart, and the clinical symptoms were more severe and unusual. Balyeat[3] claims that the differences in the weather causing the distribution and production of pollen could not account for the extreme differences in pollen content of the air.

We have found, consistently, that the freely carried pollens which are light and can be wind borne, are definitely less in the air during and after a rainfall. There is always a definite drop in a daily curve where there has been precipitation. We do not claim that climatic changes are the sole cause of diversified seasonal symptoms, rather would we emphasize that the potency of the pollen crop is the important factor, but that changes in weather, etc., must be reckoned with and considered in producing the changes in the potency of the pollen. That there is also a mechanical factor of getting the exciting substance to the mucous membranes where it can manifest itself must be considered as well.

Both botanists and allergists agree that soil content, the nitrogen content of the specific protein produced, of air and ground, the actin-

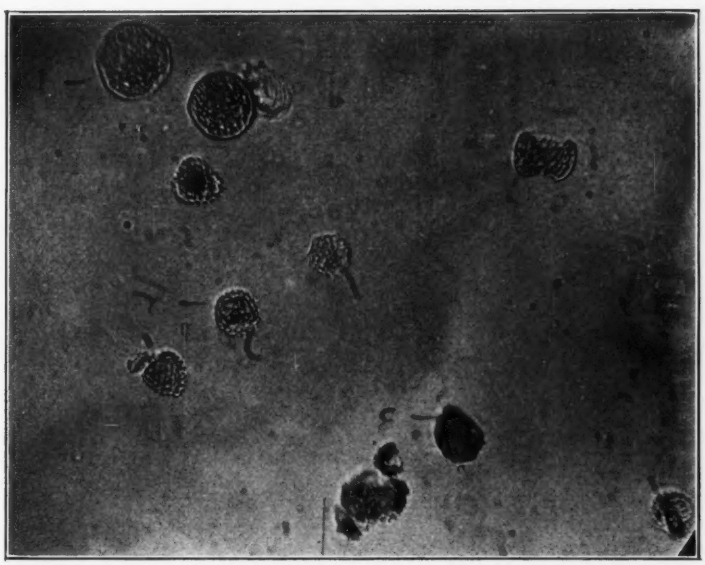

Fig. 2.—Pollens: (1) plantain; (2) ragweed; (3) goldenrod.

ate rays of the sun, and the microbiologic inhabitants of the fields all combine to produce crops of pollen which are not only variable from season to season but in portions of the same season. The potency of the pollen, therefore, is dependent in a degree on the various climatic changes.

In identifying pollens, the common ones are readily distinguished so that an amateur with a little practice can tell the important ones, one from another. Plantain, the ragweeds, and goldenrod were the ones most prevalent and recorded. While we have found goldenrod to be the offending pollen in only about 5 per cent of cases, it is one of the heavier pollens and was chosen as a comparator, since it pollinates later in the season. Fig. 2 a photomicrograph of a field taken at

random from a slide which shows all three of the recorded pollens; these are identified as: (1) plantain, (2) ragweed, (3) goldenrod.

The seasonal variation can be seen from the following charts which daily counts and are self-explanatory. Chart 2 is a composite of the three years' total counts. The locations have been the same and are, therefore, comparable. These we feel give us a clue to the differences experienced in these years for the clinical symptoms.

The second portion of this experiment was to determine the pollen content of air over a period of twenty-four hours with regard to the

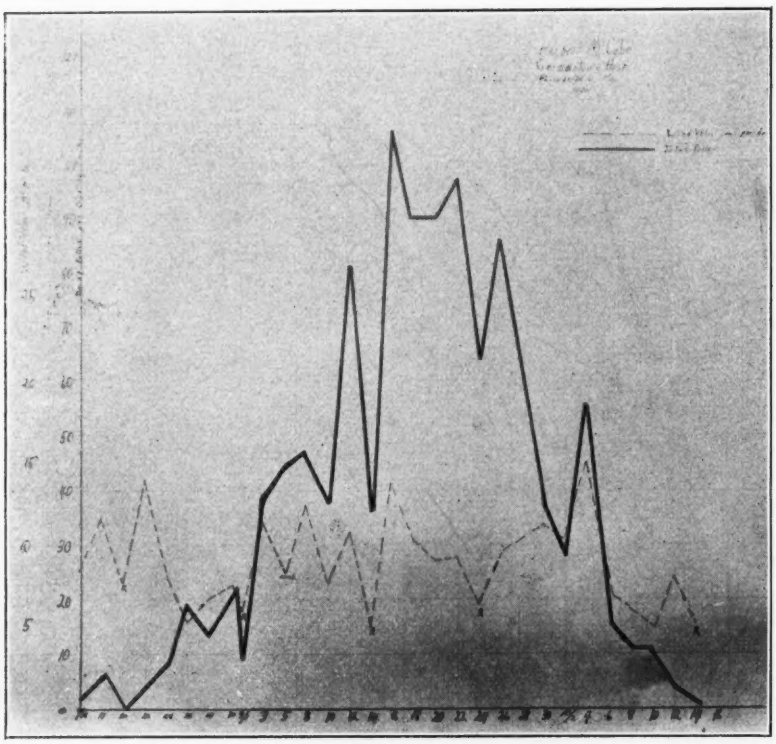

Chart 1.—Daily pollen counts 1930, Philadelphia, Pa.

temperature changes. This was correlated with height. It has always been a question whether or not the hourly changes in temperature affected the pollen content. As the earth cools after sundown, and the heavy, cooler layers of the air settle to the ground, the pollen grains settle with it, either carried down by the cooling air or the condensation of the moisture around them. It has been thought that this may, in part, be responsible for the extreme attacks between the hours of 3 and 5 A.M., especially in asthmatics.

A sixteen-story building, the Mayfair House, in Philadelphia, was chosen for this part of the experiment. It is constructed in the shape

of a double Maltese cross and has a fire exit at every floor, exposed to the outside so that it offered no complications of a courtyard to be overcome. This apartment is located in the residential section of Germantown, Philadelphia, and borders on Fairmount Parkway so that there is always a large amount of pollen in the air in that particular vicinity. Slides were exposed on each floor every two hours for a two-hour period for the entire twenty-four hours and the counts tabulated. September 18-19, 1930, from noon to noon was taken as being in the height of pollination, and the weather forecast was clear; two other attempts had been spoiled by rainfall.

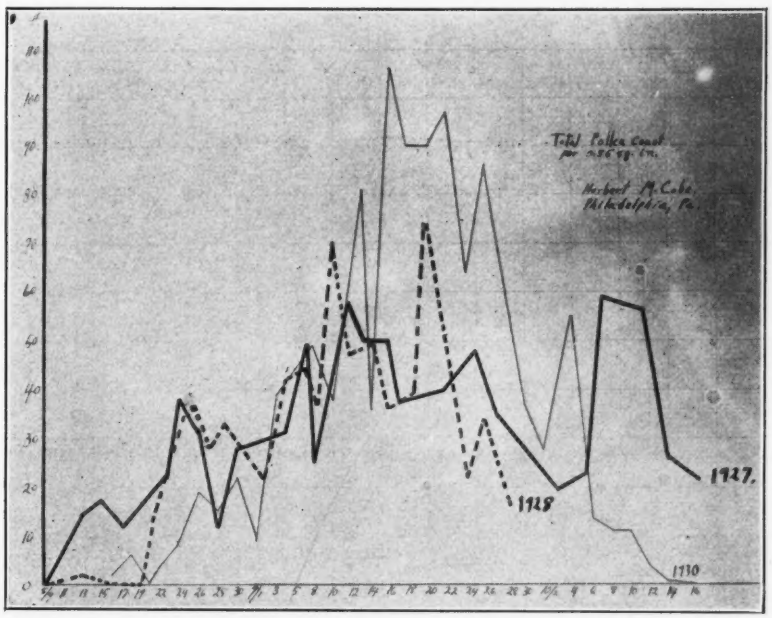

Chart 2.—Composite chart for three years, Philadelphia, Pa.

In a survey of this type, there are many things to be considered as outside factors which influence the counts and the interpretation of results. One must take into consideration temperature changes, wind velocity and direction of the wind changes, conduction and convection currents caused by draughts against the building, electric fans and ventilators. A general idea was obtained, however, and some conclusions are possible. For example, it was brought out that in a survey of this nature, the top and upper floors of a building were not practicable to record counts. The wind currents sweep up and over the building with such force and velocity that there was little or no deposition of pollen. The peak of the pollen content was approximately the center of the building but that again may be due to currents which carry pollens up to and down to the center. Likewise, currents come over the top of the building from both directions so that counts from

the tenth to the sixteenth floors are not representative. The variation from the center of the building down to the ground was not very great, although the variation from the top to the center was greater. Temperature variation for the day was nine degrees Fahrenheit. Varying from 63° at 5:30 A.M. on the 19th to 72° at 3:30 P.M. on the 18th. The total low counts occurred from 5:30 to 9:30 P.M. The drop took place from sunset until 3:30 A.M. when the counts rose rapidly and maintained a high level.

TABLE I

HOURLY COUNTS BY FLOORS
MAYFAIR HOUSE, PHILADELPHIA

FLOOR	11:30 A.M.	1:30 P.M.	3:30 P.M.	5:30 P.M.	7:30 P.M.	9:30 P.M.	11:30 P.M.	1:30 A.M.	3:30 A.M.	5:30 A.M.	7:30 A.M.	9:30 A.M.
16th	5	6	6	5	5	8	10	6	4	5	6	9
15th	7	6	7	5	8	8	9	3	3	3	8	8
10th	6	7	7	5	7	2	8	3	7	6	10	8
9th	7	8	7	5	7	5	5	3	8	11	7	5
8th	9	14	19	12	10	5	10	6	5	12	14	5
7th	4	7	8	9	6	5	4	4	7	9	10	10
6th	5	5	7	7	10	5	5	4	6	17	7	6
2nd	6	11	9	7	8	6	8	10	7	10	9	7
1st	9	6	7	9	6	7	7	11	6	10	3	17

SUMMARY

1. The amount of rainfall affects the pollen content of the atmosphere, which in turn determines seasonal variations in symptoms.

2. The year 1930, being a so-called "drought year," produced a different type of pollen which exhibited more potency as a stimulant, the height of pollination occurred later in the season, the peak of maximum atmospheric pollen content occurring later and lasting longer.

3. An experiment to determine the effect of height and temperature with the pollen content brought out the obstacles encountered in using large buildings, but a single observation showed that the atmospheric pollen content is less as the earth cools.

We offer no definite conclusions as the result of this experiment. It is presented as being an interesting variation in the routine pollen surveys. Inasmuch as it was only attempted once, it is presented here so that others may follow it further and ascertain its definite value.

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DESENSITIZATION TO FOODS*

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DESENSITIZATION to foods which produce allergy in the patient is of great importance. The determination of such allergy-producing foods with diet trial aided by skin reactions is possible in practically all cases,[1] though sensitizations both mild and severe to a great many foods raise difficulties at times. Desensitization to such foods is not accomplished readily, though several methods which will be discussed in this article are effective in varying degrees.

1. ELIMINATION OF FOODS FROM DIET

At present this method is necessary for satisfactory relief from allergic symptoms caused by specific foods. Such elimination must be absolute and the patient and physician must be sure that minute amounts of the excluded foods are not taken. Such care is absolutely necessary where marked allergy exists. When mild sensitizations are encountered, small amounts of food may be tolerated. Partial or complete desensitization with such elimination may occur in from a few weeks to several months. Such desensitization may last from a few weeks to several years. Possible breaking down of tolerance to a specific food which is being taken again by the patient must be looked for. Excessive amounts of such foods may reestablish sensitization.

Such desensitization from the elimination of foods may never occur and is rarely complete. This may be due to the occasional inclusion of such foods in the diet. Usually it depends on the degree of allergy present. In spite of this, elimination of foods at present is the most valuable method for increasing tolerance to foods.

Many infants, children, and adults have inherent dislikes for foods to which they are allergic. Young infants often refuse foods, such as milk or eggs, to which they are sensitive. This undoubtedly aids in desensitization. It is also well known that certain children with increasing age become less sensitive to foods which are continually eaten, as evidenced by clinical symptoms and skin reactions. The disappearance of reactions in a child with asthma with the total exclusion of egg for six years from the diet is shown in Table I.

TABLE I

AGE—	1 YR.	2 YR.	3 YR.	4 YR.	6 YR.	7 YR.
Egg—Whole	+++	+++	+++	+++	0	0
Egg—White	+++	++	++	+++	0	0
Egg—Yolk	++	++	++	++	0	0
Egg—Ovomucoid	0	+	0	+	0	0

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

2. ORAL DESENSITIZATION

Successful reports from the feeding of minute amounts of a food in gradually increasing doses have been made by Schofield,[2] Schloss,[3] Walker,[4] Stuart and Farnham[5] and others. In 1912, Schloss reported success with the feeding of egg, beginning with a dose of 2 mg. of ovomucoid followed by gradual increase up to 7 grams or more a day. In 1920, he stated that 12 patients had been desensitized from three to seven years to specific foods by the oral method. He recommended a 1/20 drop of milk as an initial dose with gradual increases over a period of three to six months.

An instructive report of desensitization to milk in an infant was made by Park.[6] The fact that the initial dose of 1 drop was tolerated without serious reaction in this patient showed that the milk allergy was mild in degree. My experience coincides with the recommendations recently[7] made that at times 1/1000 or even 1/10,000 of a single drop of egg or milk must be the initial dose, and that gradual increases over a period of six months to one year are at times necessary. With such therapy, skin reactions may gradually disappear. When the increase is too rapid, allergic symptoms develop and the desensitization is apt to be retarded.

In general, results from oral desensitization have been disappointing in my experience and in that of other allergists.[1]

3. HYPODERMIC DESENSITIZATION

Such treatment may be carried out with Coca's extract of the food or with a 2 to 5 per cent extract of a dry allergen in sterile salt solution or in a glycerin-salt extracting fluid. The method of treatment is the same as with pollen extracts, the initial dose being 0.1 c.c. of a dilution which just fails to produce a skin reaction. Results from such desensitization have not met the expectations of various allergists.[1, 4] However, Cooke in 1922[8] and Rackemann[9] in 1928 reported benefit from hypodermic therapy with egg extract. Campbell[10] in 1926 treated a four-year-old child for seven months so that small amounts of egg were tolerated. The skin test was originally positive to 1 to 100,000 dilution, so that his initial dose had to be 0.1 c.c. of a 1 to 1 million dilution.

If desensitization results with this method, further improvement may be obtained by gradually increasing amounts of the food by mouth. The daily administration of the food to maintain induced tolerance is also advisable.

4. PEPTONE THERAPY

Biedl and Kraus,[11] in 1909, found that peptone prevented anaphylactic reactions in animals. In 1911, Lambert, Aucel and Bouin[12] showed

that the ingestion of a small amount of a food, drug, or peptone one hour before meals prevented subsequent allergic reactions. A non-specific effect from peptone moreover was indicated by the experiments of Besredka,[13] Richet and Grineff. Good results from oral peptone therapy were reported from Pagniez, Vallery-Radot, and Nast,[14]

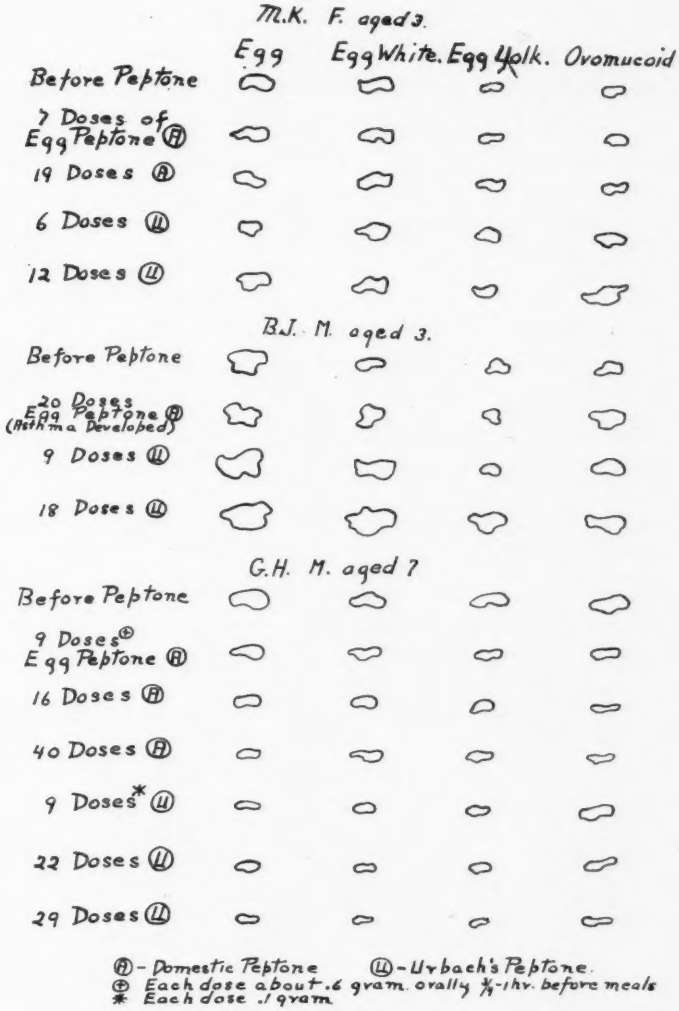

Fig. 1.

Widal, Abrami and Brissaud,[15] Auld,[16] and others. In America, Miller and Raulston[17] reported benefit from the intravenous use of peptone in patients with migraine. Such intravenous therapy however produces occasional shock and has been discontinued in my work. Ramirez,[18] after a careful study of peptone therapy, concluded it was of no value in allergy. Auld[16] and especially Luithlen[19] also reported

many bad results which the latter suggested were due to the nonspecificity of the peptone. Urbach[20] continuing the work of Luithlen has reported relief of dermatoses due to food allergy by the use of such specific peptones.

Urbach's report that the skin reaction to the specific allergen is not attainable three-quarters of an hour after the administration of its specific peptone is of interest. Local reactions in the sclera, conjunctiva, and nose resulting from the instillation of egg into the eye were also prevented by such peptone therapy. I have studied the effect of egg peptone on the skin reactions to egg in four children. Data on three of them are presented in Fig. 1. A domestic peptone was first given to these patients. Urbach's peptones were administered later. No influence on the skin reaction from either peptone was noted in three of the four patients. In G. H. the skin reactions to all of the proteins diminished. However, the rapid disappearance of the reactivity of the skin as described by Urbach after one dose of his peptone was not demonstrated in my patients, even after many doses. In one patient, skin reactions to potato were not changed after 24 oral doses of its specific peptone.

TABLE II

SYMPTOMS OF PATIENTS RELIEVED BY ELIMINATION DIETS WHICH EXCLUDED MILK AND OTHER FOODS. THESE SYMPTOMS REAPPEARED IN THE INDICATED TIMES WITH THE ADMINISTRATION OF 5 TO 10 GRAINS OF MILK PEPTONE* THREE-QUARTERS OF AN HOUR BEFORE MEALS

SYMPTOMS	SEX	AGE	DAYS OF ADMINISTRATION BEFORE SYMPTOMS APPEARED
Perennial hay fever Bronchial cough	M	12	1 Week
Nausea, gagging Generalized aching	M	30	1 Week
Allergic toxemia Generalized edema Leucorrhea	F	40	5 Days One month required to entirely recover
Diarrhea, cramping	M	45	5 Days
Fatigue, drowsiness Bad breath, fever	M	10	5 Days
Bronchial asthma Bronchitis, irritability Nasal congestion	F	9	4 Days
Bronchial asthma Coughing	F	5	6 Days
Headache, nasal congestion, pressure and weight in epigastrium	F	42	7 Days

*This peptone was shown by guinea pig experiments to contain milk protein.

My observations on the effect of specific peptones on the symptoms of the various manifestations of food allergy continue and no conclusions are now possible. Domestic milk peptone was given two patients with eczema which was caused by milk. Five to 10 grains were given three-quarters of an hour before meals for five days, and milk was then added to the diet. Eczema which had been relieved on a milk-free diet and had been reproduced by the taking of milk has not returned in six weeks in one patient and in four weeks in a second patient. This seems to substantiate Urbach's conclusions in regard to the effect of specific peptones on dermatoses due to food allergy. However, the tabulated symptoms in Table II were reproduced by the taking of the same domestic peptones before the addition of milk itself. These results indicated that the peptone was not free of milk protein. The production of typical anaphylactic shock by the injection of 0.2 c.c. of a 10 per cent solution of this peptone intracardially in a milk-sensitized guinea pig substantiated this possibility. Similar studies for the presence of protein in the specific peptones of Urbach are now in progress.

This discussion of Urbach's work offers no conclusions except that the reactivity of the skin to egg and potato have not disappeared with the continued administration of the specific peptones. The possibility of desensitizing to foods with such peptones in patients with any of the manifestations of food allergy cannot be determined at present. The preparation of specific peptones which are free from all the original protein is now in progress. With such peptones, further studies of their value in desensitization to foods will be possible.

5. DENATURIZATION OF FOODS

It has been assumed that the heating of foods modifies the protein molecule, so that its allergic response is prevented. Walzer[21] found that heated foods when ingested gave smaller and less rapid reactions in sensitized areas of skin than did unheated foods. Good results from such denaturized foods have been reported by Laroche, Richet, and Saint Girons,[22] Talbot,[23] Ratner[24] and others. However, Talbot, in 1918, reported failures with such heated foods. Hill and Stuart,[25] in 1929, noted inability to tolerate heated, dried as well as lactic acid milk, and my experience with heated foods has been disappointing, especially in food allergy in older children and adults. On the basis of Kerley's[26] recommendation that milk be heated for many hours or be superheated, a recent superheated milk has been commercialized. This product, however, produces immediate anaphylactic shock in guinea pigs sensitized to milk. It is my opinion that animal experiments should be used for the determination of the availability of such modified foods for the control of food allergy.

6. GENERAL MEASURES FOR THE DECREASE OF ALLERGIC REACTIONS

The use of calcium, quartz light, vitamin therapy, nonspecific protein therapy in the form of vaccines or serum and autohemotherapy for the reduction of allergic reactions are of no definite value. The effect of humidity on the permeability of mucous membranes, as reported by Arnold,[27] helps to explain the well-known effect of dry climates on symptoms due to food allergy.

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(For discussion, see page 81.)

DRUG IDIOSYNCRASY*

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WHILE cases of drug idiosyncrasy or allergy have been known for many years, new cases of intolerance to old and to new medicinal agents are being reported quite frequently. Most of these reports differentiate between the ordinary toxic effects of the drug and the unusual symptoms to which we give the name "idiosyncrasy"; these symptoms may come on with amounts of the drug too small to be explained by the ordinary toxicity of the drug.

The symptoms in these cases are strikingly similar even though the causative medicine may differ. They are chiefly those of urticaria and angioneurotic edema and may be very severe. Less commonly asthma, rhinitis, or eczema may occur. Certain patients may react by high fever.

In their recent book on urticaria, Pasteur Vallery Radot and L. Rogers[1] emphasize their colloidal shock theory which they claim is as true in drug idiosyncrasy as in other forms of allergy or anaphylaxis. The cardinal symptoms of this shock are hypotension, leucopenia with inversion of the leucocyte formula, lessening of blood platelets, and hypercoagulability of the blood. However, one of their antipyrine cases had leucocytosis instead of leucopenia.

Since the symptoms caused by these drugs are identical with those due to the ordinary antigens (animal danders, foods, pollens, etc.), it is most reasonable to believe that the mode of action must be similar in these groups. For many years it was hard to understand how a simple drug like aspirin could act like a complex protein, such as egg-white or ragweed pollen, but the theory of Landsteiner[2, 3] seems to have cleared this up. He pointed out that simple substances, even elemental metals, can combine with proteins, e g., blood serum, to form new immunologic compounds which act as specifically as does egg-white.

A search of the recent literature on idiosyncrasy to drugs has revealed some interesting facts. The chief medicines which can cause these symptoms are the coal-tar derivatives, ipecac, cinchona, the arsenicals, and opiates; other drugs are less commonly reported.

COAL-TAR DERIVATIVES

The coal-tar agents are probably most important because of their universal use, and cases of hypersensitiveness to these drugs are

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, Pa., June 8, 1931.

numerous. An interesting phase is that almost as fast as some pharmaceutical house introduces a new member of the group some one reports one or more cases of idiosyncrasy to that drug. Thus we have case reports regarding veramon, which is a combination of amidopyrine (pyramidon) and barbituric acid (veronal). Lilienstein[4] reported the case of a man who took 0.8 gm. of veramon and in ten minutes had severe itching, redness, and swelling of the genitalia. This man had previously taken pyramidon without trouble, but refused to be tested with veronal separately.

Haas[5] told of another man who took some of this same drug with similar angioneurotic edema of the genitalia. This man had previously taken pyramidon and veronal separately, and Haas thought he must have been sensitive to the combination and not to either drug separately.

Fechner[6] reported two more cases of severe angioneurotic edema and urticaria caused by taking veramon tablets, but Ortloph[7] pointed out that these two persons had eaten fish just before taking the medicine and he believes that the symptoms were due to a combination between the drug and broken-down fish proteins. He quotes Schlade "who has shown that when amino-acids combine with substances containing purin, a stormy combination forms with elimination of an amine group and carbon dioxide and the formation of aldehydes in the next lower carbon group. This combination is easily broken up with stormy symptoms." Fechner's two patients had each taken the drug previously without trouble.

AOLAN

Ortmann[8] has recently published a case report of a man who was given intragluteal injections of aolan for indurative acne. The fourth injection was given eight days after the third and was followed in thirty seconds by a typical anaphylactic shock, shown by severe dyspnea, cyanosis, and collapse lasting about a minute, followed quickly by pallor and then angioneurotic edema of the face. The swelling persisted for five days.

ALLONAL

Allonal, the well-known pharmaceutical preparation, is a mixture of amidopyrine and barbituric acid. Several cases of idiosyncrasy to this drug have been recently published. Crohn,[9] of Germany, has just reported serious trouble in himself. In 1927, he took two allonal tablets and the next morning he had generalized urticaria and edema of the genitalia which lasted eight days. In 1929, he took one tablet of leval, a similar preparation, for headache, with similar results, though not so severe. In 1930, he took a capsule of somnacetin, which is a combination of barbituric acid, phenacetin and codein; the next morn-

ing he had extremely severe urticaria and edema of the genitalia with extreme pruritus, followed by local abscess formation; then pains in the joints. The whole process lasted five weeks. Previously, Dr. Crohn had tolerated pure veronal and pure pyramidon. He had not tried phenacetin alone and thought best not to. The interesting feature was the localization to the genitalia.

CASE REPORT

(Hypersensitiveness to pyramidon)

I wish to add an interesting case to this group.

A dentist, aged thirty-six years, came in for hay fever treatment in August, 1930; his symptoms were typical. Skin tests were strongly positive for ragweeds. Routine protein tests were also made and were negative. January 31, 1931, he had a tooth pulled, with novocaine anesthesia. After the extraction he took three allonal tablets and the next day he took one or two aspirin tablets. He awoke the next morning with marked swelling of the eyelids, cheek, and lips, and blotches on the forehead and palms of the hands. This was followed by slight intermittent swelling and generalized fatigue. He had taken aspirin on many occasions without harm and had also had novocaine anesthesias previously without symptoms. The allonal was almost certainly incriminated here. Twelve days after the tooth was pulled he had fever and took about six grains of pyramidon; the next morning he had a severe recurrence of the angioneurotic edema. Each allonal tablet contains one and one-half grains of pyramidon; this made the diagnosis of idiosyncrasy to pyramidon fairly certain. Skin tests to twelve different compounds, including aspirin, phenacetin, pyramidon, and allonal were negative. Passive transfer was not attempted because of the well-known lack of success.

Other coal-tar derivatives have frequently caused allergic symptoms, especially aspirin, phenacetin, antipyrine, and luminal. Aspirin is a rather common cause of attacks of bronchial asthma, and I have several patients who have warned me against prescribing this drug for them.

QUININE

The cinchona derivatives are frequent trouble makers and the literature abounds with case reports of hypersensitiveness to quinine. Among others we may quote the cases of Cruikshank[10] and Gray.[11] They each injected 0.13 gm. quinine hydrochloride into patients with varicose veins. Each patient had a prompt and stormy anaphylactic shock, almost to the point of death. Scratch tests after recovery were strongly positive in each case. These cases illustrate the danger of using quinine solutions in injecting varicosities.

Burgess and Usher[12] have recently reported cases of dermatitis of the face caused by sensitiveness to the quinine used in after-shave lotions in Canada. Patch tests were positive. The authors advise that quinine be omitted from shaving lotions.

An interesting observation along this line was made by Dawson and Garbade.[13] They pointed out that patients who are sensitive to cin-

chona products show this allergic reaction only to the levorotatory alkaloids of cinchona. Thus, the patient reacts to quinine, which is levorotatory but is negative to quinidine. This immediately points out the wisdom of using quinidine in patients who cannot tolerate quinine.

The toxic and allergic symptoms due to quinine are easily differentiated. The toxic effects are tinnitus, vertigo, and nausea and vomiting. The allergic symptoms are those of urticaria and angioneurotic edema.

OTHER DRUGS

Idiosyncrasy to ipecac and emetin, to complex arsenicals, e.g., salvarsan, and to opiates, e.g., codein, are well known and frequent. Other drugs, such as bromides, mercury, and copaiba can also cause trouble along this line.

PASSIVE TRANSFER

Search of the literature has revealed no case of successful transfer of idiosyncrasy to drugs from man to man. The few cases reported as succeeding have been from man to animals. M. Lang,[14] in 1927, reported transfer of sensitiveness to quinine from a patient to guinea pigs, but his work does not seem convincing. Thiers and Rousset[15] transferred blood serum of a patient who was hypersensitive to sodium salicylate. The serum was injected into the hearts of seven guinea pigs. Later, four of these were injected with sodium salicylate and two of them died with typical anaphylactic reactions. These experiments seem more convincing.

TREATMENT

The treatment of drug idiosyncrasy is mainly preventive—avoidance of the offending medicinal agent. But even this is not as simple as it would seem, for new pharmaceutical products are being introduced in large numbers and patients are reacting to some of these new drugs. We must all do our best to shield our allergic patients from these new products until we are sure no harm will result.

Certain drugs, however, are so important as to prompt us to try to overcome the idiosyncrasy of the patient. Salvarsan and similar products have been successfully given by the method of small intradermal doses preceding the larger ones. But there is great danger here in that even the temporary desensitization may not occur.

Hypersensitiveness to aspirin and antipyrin may be overcome by feeding small amounts first, as in the case reported by Widal and his assistants.[16] Van Leeuwen[17] believes that 10 per cent of all asthmatic patients are sensitive to the aspirin group. He thinks that desensitization by injection or ingestion is difficult to obtain and may be quite dangerous, and he advises complete avoidance of these drugs.

It has already been pointed out that in cases of hypersensitiveness to quinine, it may be well to try its isomer, quinidine.

SUMMARY

1. Idiosyncrasy to drugs is widespread and is probably on the increase, as new pharmaceutical products are being introduced.

2. Coal-tar derivatives are most important, as they are widely used.

3. A case is reported of hypersensitiveness to amidopyrine taken as allonal and pyramidon.

4. Passive transfer of drug idiosyncrasy from man to man has been unsuccessful to date; from man to animals partially successful.

5. The best treatment of hypersensitiveness to drugs is absolute avoidance.

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Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

NINTH ANNUAL MEETING, PHILADELPHIA, PA., JUNE 8 AND 9, 1931
(CONTINUED)

Desensitization to Foods. ALBERT H. ROWE, OAKLAND, CALIF. (For original article, see page 69.)

DISCUSSION

DR. WARREN T. VAUGHAN, RICHMOND, VA.—A little over a year ago Dr. C. Ulysses Moore, of Portland, Oregon, who was in Urbach's Clinic at that time, wrote me about the work on specific peptones, and I tried this out in one case of a child who was sensitive both to egg and to wheat. I did it apparently in the same way that Dr. Rowe did, although I may have misunderstood him. That is, the test was not necessarily done one hour and a half after the administration of peptone. In those two instances, the first with egg and second with wheat, I found no diminution of the skin test reaction, nor was there any subjective improvement. The child was off of the wheat and egg the first part of the time and during the last half was eating them.

Dr. Moore is with us here today, and I hope possibly he will have something interesting to say from his observations in Urbach's Clinic.

DR. C. ULYSSES MOORE, PORTLAND.—Dr. Urbach is a very able man, as those of you who know him can testify, and he is doing very original work along the lines of allergy. I believe that his book, when translated and published in English, will have some valuable ideas in it.

In his skin clinic, he is likely to make a forcible statement about the value of his "Propeptan" for a certain child. It does not always work, although in a good percentage of the cases that he showed us he did get very satisfactory results. He admits that it is still in the evolutionary stage, but believes that he has the right principle. To this we agree and in consequence are trying out his product in our clinic.

DR. E. L. SHERRER.—I think there are two reports in the literature which may have a bearing on the method of study and results obtained by Dr. Rowe in the treatment of food allergy. One report is by Levine and Coca to the effect that positive skin reactions persist after treatment by desensitization to an antigen even though symptoms are absent when the patient is exposed to large quantities of the antigen. It would seem, therefore, that the relief from symptoms rather than the decrease in skin reaction should be used as a criterion for the efficacy of treatment.

The other report is by Gobell and his coworkers at the Rockefeller Institute. They showed that sensitized animals could be protected from anaphylactic shock for several hours by the injection of split-off portions of the antigen. It would appear possible that peptone therapy in food allergy acts in a similar manner, that is, the peptone being a split antigen might inhibit for several hours the development of allergic reactions.

DR. BALYEAT, OKLAHOMA CITY.—The very fact that a child may be extremely sensitive to wheat, eggs or milk, or any other food, and in two or three years' time clinically lose that sensitivity, is excellent evidence that we ought to be able

orally to desensitize patients who are sensitive to food. At the present time we have a fairly large group of asthmatic and eczematous children on whom we are trying to produce desensitization by the oral method, and we find that it has been quite satisfactory. In migraine, however, our experience has not been quite so good. It seems to me that we all should study the problem of the oral method of desensitization in cases of food sensitivity, as certainly it is the most logical one.

Allergy in Duodenal Ulcer. Richard A. Kern and Sloan G. Stewart, Philadelphia, Pa. (For original article, see page 51.)

Allergic Colitis. C. Ulysses Moore, Portland, Oregon. (Abstract.)

The writer stresses the importance of the consideration of a possible allergic etiology in colitis of acute or chronic type. Two case reports are given in detail. In the first case, the patient, a child of six years, had suffered from diarrhea for a period of over five years, during which time she had been under treatment in various hospitals with no satisfactory results. When seen by the writer, she was in a state of extreme emaciation. Stool study revealed mucus, pus, streptococci and a diplobacillus. Skin tests showed a strong positive reaction to egg and weaker positive reactions to several other foods. It was recalled that when the patient was nine months old, the ingestion of egg caused vomiting and thickening of the tongue. The patient when seen by the writer was in such condition that treatment proved ineffectual and within three weeks she died. It is strongly suggested that had the allergic basis of the complaint been discovered in infancy, the outcome might have been very different.

In the second case, that of a man aged forty-six years, in whom there had been a history of hay fever and asthma from the age of twelve years, colitis of the mucous type had existed for one year, with pain in the right lower abdominal quadrant and an almost continuous sense of pressure in the epigastrium. Stool study revealed a low gram-positive bacteria count, the presence of streptococci and staphylococci and a small amount of mucus. Skin tests (scratch and intradermal) showed positive reactions to several foods and to orris root, cotton seed, horse and cattle hair. Treatment consisted of the avoidance of contact with those substances to which the patient had been found sensitive and the giving of a protein-free culture of Bacillus acidophilus. Excellent results were obtained.

The author points out that intestinal upsets are very common in food-sensitive children. The inflamed mucosa are particularly susceptible to bacterial attack. For this reason, ulcerations may be superimposed on the allergic condition. Cases of allergic colitis recover more quickly if, in addition to the reacting foods, the colonic flora are kept normal.

Drug Idiosyncrasy. Leon Unger, Chicago, Ill. (For original article, see page 76.)

Some Allergic Factors in Essential Epilepsy. RALPH H. SPANGLER, PHILADELPHIA, PA. (For original article, see page 39.)

DISCUSSION

DR. JOSEPH L. MILLER, CHICAGO.—I was very much interested in the paper on peptic ulcer because about ten years ago or perhaps less Dr. Pribam in Germany reported on the treatment of gastric ulcer by the use of what he called nonspecific protein therapy, using vegetable protein given intravenously. He made no modification of diet, and he claimed to have gotten striking results. The pain disappeared, and, after a period of time, the ulcer, as far as the x-ray picture could show, disappeared. At that time Pribam was over here, and he thought he had something specific in the vegetable protein. We tried a number of people with gastric ulcer and with typhoid, intravenously in small doses. We did not change the diet, and I was perfectly dumbfounded at how the pain promptly disappeared in these patients.

We did not attempt to treat them for a long period, but we did observe that the pain stayed away perhaps a week after the protein was discontinued. It then returned.

There had been many reports in this country confirming the work of Pribam that ulcer can be treated with a foreign protein. There is nothing to explain how this helps and no one has suggested, so far as I know, that this might have been due to nonspecific desensitization.

In regard to the paper on colitis, that is a very interesting subject. Many years back attention was called to the relationship between the so-called spastic and mucous colitis and asthma. I was very much interested in Dr. Moore's report on allergic colitis which has been suspected as being related to asthma. It was most unfortunate that it was called mucous colitis. The term "colitis" is a misnomer, and I hope this association will be able to get a name for this disease which will omit the "itis," and perhaps introduce something to indicate that it is allergic.

I shall speak of Dr. Spangler's work a few minutes. I believe epilepsy is an allergic disease. I want to bring out this one point: When Spangler's first paper appeared, he referred to an account in some medical journal, of a case of confirmed epilepsy that was cured after the man was bitten by a rattlesnake. I was able to obtain that journal. I do not remember the name of it, but it interested me because it showed the scientific interest of this presumably country practitioner in Texas. This man, a patient of his for years, was bitten by a rattlesnake, and he had been free from asthma for several years.

He had another epileptic patient and this man consented to be bitten. There was some delay in getting a rattlesnake, though I understand they are abundant in Texas. Meanwhile a great deal of publicity had arisen in regard to it, and when they did get the rattlesnake, the man refused to be bitten. The doctor made an apology for reporting the case, stating, "I am reporting this little affair that occurred so perhaps somebody else with opportunity may be able to take it up and carry it farther," and that Dr. Spangler did.

DR. GEORGE PINESS, LOS ANGELES.—I do not feel that Dr. Moore's paper presented typical cases of allergic colitis for several reasons: first, both individuals had other complicating conditions that might present the same train of symptoms; second, they were treated by many nonspecific methods and with little result, no proof having been offered that specific treatment was tried alone before the other treatments were instituted.

I should like to ask Dr. Unger why he considers aolin belonging to the group of so-called idiosyncrasies. It is my belief and opinion that this is merely a milk

albumin, and I should also like to ask the essayist what his technic is and the character of the reactions that result when testing with drugs.

DR. MARION SULZBERGER, NEW YORK.—There is so much to be said about the papers which we have just heard, yet I want to take only a minute to voice some of the things I should like to remark concerning them. One is the question of the different allergies in different organs, brought forth today; for instance, the duodenal ulcer, the colitis and the epilepsy bring up the question of different local centers of sensitivity in different organs. The substances causing these various changes come in contact with every organ, and there must be a localized area of hypersensitivity in a specific organ which makes that and that alone react to the allergen. In this connection I may remark that last week I listened to a paper by Dr. Fishberg on nephritis. He came out flat-footedly with the statement that glomerular nephritis was probably due to a hypersensitivity of the glomeruli.

This varying localization of allergy is well demonstrated in the skin. For instance, even in the skin itself one can see a distinct localization of hypersensitivity, in the epidermis alone and not affecting the cutis in any way. One sees cases in which a contact test with a substance causes terrific reaction in the epidermis and still the application of this same substance through the epidermis into the cutis causes no reaction whatsoever. We have here again a sharply limited, circumscribed hypersensitiveness of a certain organ or part of an organ.

That is well brought out in the drug eruptions. One of the most frequent ones that we find, and which I am in a position to see almost every day, is the kind in which there is a *fixed drug eruption*, that is just a certain circumscribed area of the skin that keeps reacting upon ingestion of the drug. Only one little spot may keep reacting, in spite of the fact that the drugs must be distributed approximately equally to the whole skin.

It seems that the simple chemicals, the nonproteins, are much more prone to affect the epidermis than the more complex substances, and we see dermatitis which can be demonstrated only by patch testing. One of the most frequent causes of those is the fur dyes, the paraphenylendiamine group. There are in addition to these eczematous eruptions many other drug eruptions which probably only the dermatologist can see, such as the erythema multiforme type, erythema nodosum type scarlatiniform and morbillaform types, etc.

DR. M. MURRAY PESHKIN, NEW YORK CITY.—The title of Dr. Unger's paper led me to believe that only drug sensitization of the ingestion type was to be considered. However, after listening to the paper, I believe a discussion of drug sensitizations other than by ingestion is in order. It was stated that a careful survey of the literature has been made. However, reference to papers appearing in 1923 by Berton, in 1925 by Rackemann and in 1924 by myself among others, have not been mentioned. My paper dealt with "Bronchial Asthma and Other Allergic Manifestations in Pharmacists." It covered the contact and inhalant manifestations of allergy due to a variety of drugs. A survey of the large chemical and pharmaceutical houses throughout this country was made in addition to reporting two unusual cases of drug sensitization—rhubarb and lycopodium.

Dr. Unger also made the statement that the literature shows no instances of successful passive transfer with drug sensitization. Biberstein in 1926 reported positive passive transfers with arsphenamine, bismuth, a brand of amidopyrine, garlic, iodine, potassium iodide, acetyl, salicylic acid and acetophenetidin. Coca and Fineman and myself have successfully demonstrated passive transfer in cases of sensitization to ipecac.

DR. SAMUEL M. FEINBERG, CHICAGO.—There is one remark I should like to make in view of what Dr. Peshkin has said. There is nothing new under the sun

apparently. Speaking about ipecac, we can refer back to the old book of Salter first published in 1864. He reported among other things that we consider rare nowadays, several cases of ipecac asthma, some of them in medical students and one or two in pharmacists. I think it is worth while and of interest to call attention to that fact because many things have been referred to from time to time as rather unusual or new, and it is rather illuminating to find some of the modern observations in old texts.

DR. LOUIS TUFT, PHILADELPHIA.—I should like to ask Dr. Unger whether the case of aolan sensitiveness which he mentioned occurred in an allergic or normal individual and whether the aolan was given intramuscularly or intracutaneously.

Four years ago while injecting aolan intracutaneously into a normal individual, there developed after the fourth injection marked local manifestations, after the fifth, given about ten days after the initial injection, he went into a state of collapse and shock with a marked local eruption over his arm. I took this to be an example of acquired hypersensitiveness to aolan, very much similar, I believed, to the case reported by Dr. Unger. I have also under my care an asthmatic who is very sensitive to morphine and its derivatives—recently she was given pantopon (a synthetic morphine-like drug) and had marked reaction to it, as well as to codeine. This represents then an example of group-sensitiveness to drugs of a certain type.

DR. MOORE.—In the first place, I simply intended to give you from our experience something that has caused us to take a more varied, a polyvalent interest, if you please, in the treatment of these cases, and these two histories are intended to show that.

In the first draft of the paper I covered a point which Dr. Sulzberger mentioned, namely, that different organs are affected. I think that we can look upon that in a general way. For instance, children up to two years of age rarely have asthma. The skin alone manifests the allergic symptoms; after two years the bronchial mucous membrane and the gastrointestinal tract and the genitourinary tract become involved.

That brings up a question to my mind: Why is it that in Eastern Europe so little asthma and allergic diseases occur, whereas in Western Europe there are more, in England a good deal more, and in America still more? It seems to me there is an opportunity for some work to be done in this connection.

DR. UNGER.—In regard to Dr. Peshkin's remarks about aolan not being a particular drug, it is listed as a drug in the Index. The case of Dr. Ortmann was reported under the heading of "Drug Idiosynerasy." I realize it is a milk product and perhaps should not have been included with the other cases such as the coal-tar derivatives.

The tests which were done on the case I reported consisted of scratch tests. There was no reaction to them at all.

Dr. Sulzberger's remarks interested me very much, especially his statement that drugs reacted in a fixed area. I had not realized that. The drugs that I mention in my paper reacted by causing generalized urticaria and angioneurotic edema. I spoke of several effects, on the genitalia and elsewhere.

As to the work of Dr. Peshkin, I am very much pleased to get the information about the proved passive transfer cases. I had not come across them. As far as his article is concerned, I have read it and have a copy, but I did not include it in the paper, as I was speaking mostly of ingestant drugs. The only other drug I included was the aolan which was injected. The aolan, by the way, was injected intragluteally. No mention was made of its being an allergic case. It was followed by symptoms resembling anaphylactic shock.

DR. SPANGLER.—In closing I should just like to put on record the experience of the druggist who prepares the crotalin solution I use. He invariably, in handling the dried venom, develops acute symptoms of hypersensitivity. His eyes water, he sneezes repeatedly and develops paroxysms of asthmatic breathing. Mulfords have reported a similar experience in one of their laboratory workers who prepares anti-venom solutions.

Skin Reactions With Staphylococcus Aureus. I. PILOT, CHICAGO, ILL. (Abstract.)

During the past two years with Afremow, Kobak and B. Cohen, we have been observing skin reactions in man with staphylococci. Broth filtrates of *Staphylococcus aureus* cultivated for five to eight days excite a skin reaction in man comparable to that observed in the filtrates of *Streptococcus hemolyticus*. The potency varies with different strains, some producing reaction up to 1 to 1,000 dilution, others only at 1 to 100. Forty-seven per cent of 1,062 persons twelve to sixty-nine years of age reacted positively. The toxin is rendered inert by heating for one hour at 60° F. Of 56 patients suffering from staphylococcus infections, such as furunculosis, carbuncle, osteomyelitis, 89 per cent reacted positively, often more violently than normal persons. Among diabetic patients 52 per cent of 41 cases gave positive results. Diabetics with active infection due to staphylococcus reacted very strongly to the dilute toxin. Vaccines prepared by heating saline suspensions for one hour at 60° C. given in 0.2 c.c. of a dilution containing 2 to 5 million per c.c. gave positive tests in 49 per cent among 117 patients, of whom 46 per cent of the same group reacted positively to filtrates of same strains. Forty-eight per cent reacted to both vaccine and filtrate. Patients infected with staphylococci gave intradermal reactions with vaccines in 98 per cent. Both hemolytic and nonhemolytic strains gave skin reactions. Three to five injections of filtrate injected into persons positive to dilute toxin rendered tests negative in most instances. Antiserums prepared by injecting rabbits and horses (Parker) with toxin, neutralized the skin-reacting substance in man. Serums of persons giving negative reaction also neutralized the toxin. Passive transfer of skin sensitiveness was unsuccessful. Twenty-five persons reacting negatively were injected intradermally with the serum of seven persons giving positive test. In none was a successful skin reaction produced by the subsequent local injection of the toxin. How much of the skin reaction is due to toxin or is result of allergy still remains unsettled.

Although newborn infants are very susceptible to staphylococcus skin infections, none of 34 tested gave positive test with either filtrate (1 to 100) or vaccine. The mothers reacted positively in 88.5 per cent. Infants from the second month on began to give positive reaction in larger percentages as they grew older in months. The lack of response on the part of the newborn is apparently not associated with

a protective mechanism but is due to an inherent lack of development of the reactivity of the skin. Older infants acquire the reactivity observed in adults.

Association of Infectious Asthma and Arthritis From the Point of View of Bacterial Allergy. JOSEPH HARKAVY AND SELIAN HEBALD, NEW YORK CITY. (Abstract.)

In studying a series of 400 adult asthmatics, 47 per cent were found to be non-sensitive, their asthma being due to foci of infection in the upper and lower respiratory tract. In this entire group, nine patients observed since 1922 had, in addition to their asthma, attacks of arthritis. The ages of these patients varied from thirty-six to fifty-nine years. There were six females and three males.

The arthritis is migratory with moderate swelling, redness and pain on motion of the joints and may persist several weeks. The temperature does not exceed 99°. Certain cases show mild proliferative changes by x-ray examination in one joint as a rule, the spine or knee, which were interpreted as being due to secondary static influences. With this exception, involved joints subside with complete restitution. The patients had been asthmatic before they developed arthritis. The duration of the asthmatic state varied from six to fifty years, whereas the arthritis had existed from three months to four years. In two of our cases the transitory arthritic manifestations subsided when the asthma came to the fore and vice versa.

In four of these patients the existence of atopic hypersensitiveness to substances such as ragweed, goose feathers, dog hair, rabbit hair, as well as dust, could be definitely shown. Their elimination did not successfully influence the asthmatic attacks because equally responsible for the asthma in these individuals was infection in the sinuses or lungs. The arthritis present was interpreted as being due to foci of infection within the respiratory tract which appeared to be the sole etiologic factor of the asthma and arthritic manifestations occurring in the other six cases. In these no atopic sensitiveness could be found. The reason for believing that the arthritis and the asthma was mediated by the same foci of infection was to be found in the fact that in every case in which the pus from the antra was removed by lavage and the ethmoids were treated with argyrol tampons, etc., where focal involvement was fairly recent and readily accessible to treatment or due to an unresolved pneumonia only (in eight of the nine patients) the arthritis disappeared completely. Following the subsidence of the active focus, the asthmatic attacks likewise became less frequent and milder. During warm weather both conditions improved, indicating the general beneficent effect of temperature and climate on chronic infections.

In a discussion of the nature of the asthma and associated arthritis, the authors suggest that both are probably examples of the same mechanism, bacterial allergy accompanying infection. They therefore review the varied conceptions of allergy and their significance in elucidating certain clinical entities.

Experimental proof of bacterial allergy accompanying infection is to be found in the work of Zinsser and Grinnell with pneumococci and streptococci. These authors suggest that streptococcus allergy might bear a relationship to certain forms of arthritis associated with sterile joints. More recent work of Francis and Tillet with type specific polysaccharides of the pneumococci has substantiated to a greater extent the early observations of bacterial allergy made by Zinsser and his associates. Further studies along these lines have been made by various authors.

As a result of all this work evidence is rapidly accumulating to the effect that the allergic state is part of the immunologic mechanism accompanying infection.

In the clinic, interpretation of bacterial allergy is much more difficult. The complex reactions accompanying immunologic processes in the human beings are as yet not sufficiently elucidated. Positive skin tests with bacteria or their products do not always establish etiologic relationship between the organism and the disease under investigation. The reason may perhaps be found in the following facts (a) that proper antigenic fractions of the incriminating bacteria are not yet available, (b) there may be a relationship between protein fractions of certain bacteria and heterologous organisms which may give rise to confusing reactions, (c) invasion with living bacteria may so alter the tissues that secondary antigens may develop and be responsible for allergic skin reactions, (d) the presence of minor secondary infections in the respiratory passages or the continuous focal presence of these bacteria in the hosts may give positive reactions on intradermal injections so that reactions with so-called specific antigens may be obtained in normal individuals and be of no special significance.

In view of such difficulties, conclusions derived as to the nature of this syndrome must be based on a clinical interpretation of symptoms in the light of established experimental and empirical data. The evidence at hand which leads us to suspect that the arthritis may be of the same nature as the asthma rather than coincidental, is therefore partly circumstantial and partly factual. It is founded (a) on analogies of essentially atopic syndromes following the injection of soluble foreign proteins, such as horse serum, etc., where asthma, arthritis and urticaria may occur; (b) on the facts that infectious asthma due to allergy which is admittedly an accepted clinical entity may be associated with similar symptoms of arthritis (the allergic nature of the latter is furthermore supported by the observations of Zinsser to

the effect that "experimentally, in bacterial allergy, it appears that sensitiveness of joints can be demonstrated as to some extent parallel to general sensitiveness"); (c) on the findings that the same foci remote from the joints were responsible for the asthma as well as the arthritic symptoms (this is in line with the work of Swift, Hitchcook and Derrick, on focal infection giving rise to a state of hypersensitiveness); (d) on the observations that none of the patients showed any toxic manifestations due to the chronic foci (they were ambulatory and their temperatures rarely exceeded 99°); (e) the marked relief of the asthmatic attacks and complete disappearance of arthritis in eight of the nine cases following the elimination of the responsible foci of infection.

As a consequence of these findings it can be stated that certain individuals may develop sensitiveness to bacterial infection, the effects of which may be manifested in one or more particular distant sites, the upper or lower respiratory tract or the joints. The clinical manifestations may then be asthma or recurrent nasopharyngeal symptoms such as vasomotor rhinitis or arthritis.

The presence of two "shock organs" in the sense of Coca in the same individual may induce involvement in both. Atopic sensitiveness may coexist and when latent may be brought to the fore by an acute bacterial infection. Thus it may be primary or secondary. In per respiratory tract may evoke latent atopic hypersensitiveness.
our experience we have frequently noted that an infection in the up-

An Evaluation of the Therapeutic Effect of the Caldwell-Luc Operation in Bronchial Asthma. HARRY P. SCHENCK AND RICHARD A. KERN, PHILADELPHIA, PA. (To be published.)

Intradermal Bacterial Suspensions and House Dust Extract in Respiratory Disease. ALEXANDER STERLING, PHILADELPHIA, PA. (Abstract.)

This paper deals with allergic patients who for the most part are not sensitive to the common allergens. In this group of cases treatment with autogenous vaccines (bacterins) which usually contained staphylococci and streptococci had been disappointing. It is believed that results were due to sensitivity to some other bacterial antigen.

The work presented in the paper was based upon an observation that children who had whooping cough shortly before the development of asthmatic attacks, gave marked intradermal reactions to pertussis bacterins. Vaccines to various organisms, particularly streptococci and pneumococci, the influenza group, B. coli and *Micrococcus catarrhalis* were prepared in a conventional way. The final suspensions were 200,000,000 organisms per c.c. Intradermal tests with 0.1 c.c. to 0.2 c.c. of these organisms were used, and reactions were recorded after the first fifteen minutes to one-half hour, and again after twelve to

twenty-four hours. Many patients who had been classified in the nonsensitive group were found to give marked reactions to various bacterial antigens. These patients also gave reactions to house dust extract from their own house. From 50 per cent to 60 per cent of this group gave marked reactions either to vaccines or house dust. A control group of patients of nonallergic and noninfectious diseases were tested to bacterial allergens and house dust, but few of these gave positive reactions. Treatment with vaccines and house dust proved to be quite satisfactory. It was noted particularly that many patients with asthma and hay fever who had received such treatment were free thereafter from recurrent attacks of head colds.

Other types of respiratory diseases, such as bronchitis, head colds, etc., were likewise tested to house dust and to bacterial allergens. Many of these patients gave positive skin reactions, and treatment with these allergens gave results quite as satisfactory as those in patients with allergy so treated.

Skin reactions from intradermal bacterial proteins are of two types. First is that comparable to other allergens with a wheal, pseudopods and surrounding erythema. In most cases, however, the response was an inflammatory reaction which appeared twelve to twenty-four hours after testing. This type of reaction occurred in 70 per cent of the cases.

It was noted that attacks of asthma were accidentally induced by giving too much dust or bacterial extract in testing. Moreover, good results in about 65 per cent of the patients treated with bacterial and dust allergens were obtained. These factors speak for a specific sensitivity to these allergens. In cases where treatment was not successful, results were attributed to insufficient time allowed for the treatment and also to secondary degeneration changes in the lungs and heart. It is pointed out that a concentrated house dust extract is necessary.

The method of treatment is as follows: The first dose is one minim, and each subsequent dose is increased one to two minims until 10 minims are reached. Injections are given twice a week. At this point injections are given once a week and the doses increased gradually to 15 minims. After that, injections are given every two weeks until the dose is increased to 20 minims. This dose is continued as follows: Five injections are given at three-week intervals; then five at four-week intervals; then at five-week intervals until the patient's improvment is complete. This holds true both for the bacterial allergens (2,000 organisms per c.c.) and for house dust (concentrated).

Many charts and a colored drawing illustrate the points made in the paper.

DISCUSSION

DR. WILLIAM S. THOMAS, NEW YORK CITY.—My contribution to the discussion of the papers of Drs. Harkavy and Pilot is made from the standpoint of one

who is convinced that bacteria dwelling in a human host may act as allergens, whether they be existing latently or acting as a cause of toxic or inflammatory symptoms.

What are the essential factors that identify allergens as such?

(1) Allergens are agents capable of sensitizing certain human beings. (2) Allergens are usually organic substances containing protein matter. (3) Allergens are usually substances with which the sensitized patient is in habitual or frequent contact. (4) Allergens may produce skin reactions when brought into proper contact with persons sensitized to them. (5) Allergens may excite allergic symptoms when brought into contact with sensitized individuals. Such contact may be with mucous membrane of respiratory tract or alimentary tract or by means of subcutaneous or intracutaneous injection. (6) Allergens may, under certain conditions, in allergic patients, be associated with eosinophilia. (7) Skin sensitiveness to allergens under certain conditions may be passively transferred to normal individuals. (8) Allergens, when properly employed, may produce relief of allergic symptoms (desensitization).

Each of the above mentioned characteristics of allergens has been shown to apply to bacteria in the human host. If the truth of the above statements be admitted, it follows that bacterial vaccines properly prepared and tested in every respect may be expected to find their place as therapeutic agents in company with the ordinarily used protein extracts now widely used in diagnosis and treatment of allergic manifestations.

The records of 300 completed cases of bacterial asthma treated by vaccines according to technic of ten years development, have demonstrated that when properly used, vaccine therapy has given material relief in 68 per cent of the cases.

DR. HARRY S. BERNTON, WASHINGTON.—I have been very much interested in the charts which Dr. Sterling has shown illustrating the positive intracutaneous reactions obtained with the bacterial vaccines and with house dust. I should like to ask Dr. Sterling if a positive skin reaction with a bacterial vaccine indicates that the organism in question is responsible for "colds," perennial rhinitis, hay fever or asthma.

I should, also, like to ask Dr. Sterling whether or not he has tested a large group of nonallergic patients and normal individuals with his bacterial products. If he has not, I shall urge him to do so because the results will be startling. The laws governing asthma are entirely different from those governing infection—so different, in fact, that the possibility of pathogenic bacteria causing asthma seems remote.

The important rôle of molds in asthma is now being appreciated. In a paper, soon to be published by Dr. Thom of the U. S. Department of Agriculture and by myself, it will be noted that allergic cases hitherto classed as nonreactors or bacterial in nature are sensitive to molds.

DR. FRANCIS M. RACKEMANN, BOSTON.—The relation of bacteria to hypersensitive states is always important. There are a number of ways in which bacteria can influence our patients. As we heard this morning, typical allergy can begin with an infection. The infection lowers the resistance, and sensitiveness begins to show itself at that time.

Second, acute infections of a certain kind can bring about a remission of the symptoms. That is important because we also believe that; third, other infections of a different kind can serve as secondary invaders to make a simple process more complicated and thus to make a bad matter worse. In those three ways, bacteria are associated with ordinary allergy, and in all of them, the allergy is the primary factor.

In addition I, for one, believe that bacteria can, in and by themselves, set up a state of hypersensitiveness which can, in turn, be responsible for the asthma and be the sole factor in that asthma.

Such a theory is rather hard to prove, but it leads me to my second topic, which is the matter of diagnosis of these bacterial infections. Here the difficulties lie in the fact that we have two types of skin test for bacteria. The first is the tuberculin type of reaction, inflammatory in nature, delayed in the time of its appearance, and characterized, of course, by a redness and swelling which appears usually in twenty-four hours. This tuberculin type of reaction depends upon a previous active infection by the same organism. Mackenzie and Hangar failed to find such delayed reactions in infants, but they could easily demonstrate them in older children.

The second type is the immediate urticarial reaction best demonstrated by the specific carbohydrate as recently isolated by Avery and his coworkers at the Rockefeller Institute. I believe that the whole problem of bacterial hypersensitiveness must remain unsolved until we can test more of our patients with specific carbohydrates. That problem will be very difficult because the Rockefeller Institute reports have demonstrated that the specificity depends on carbohydrates of a particular kind; that specificity depends on chemical structure. It has been demonstrated, for example, that the carbohydrate of Type I pneumococcus is chemically different from the carbohydrate of Type II pneumococcus.

If then we are going to draw conclusions in our clinical work, I suppose we shall need to have a different specific carbohydrate for each of the different strains which we want to use.

The problem of foci of infection and of the relation of the nose and throat to asthma is in line with the above. If we assume that allergic reactions are produced by bacteria and that the chronic cases are prolonged by bacterial action, we must postulate the presence of a focus of infection in the body, and we must also postulate that the difficulty of treatment depends upon the difficulty of removing that focus in a thorough manner.

Let me remind you that the focus of infection may be not only in the antrum, where radical antrum operations will take care of it perhaps, but it may be in the ethmoids, the sphenoids, or in the frontal sinuses, or there may be local infections in the peribronchial glands, such as was demonstrated a month ago by A. K. Krause in a very interesting paper read in Atlantic City.

Finally, do not forget that in connection with arthritis, Dr. Zinsser has described at least one case in which a focus of infection was found in the spleen. If we appreciate these things, we can begin to see why we appear to disagree about so many different features of this very interesting and very important subject.

DR. PILOT.—I have nothing to add to my own subject, but I do want to say something in connection with Dr. Harkavy's paper because a great part of our work in the last year has been the relationship of hemolytic streptococci to arthritis with particular reference to the rôle of hypersensitiveness.

In some of our work that we did with septic sore throat in connection with a particular streptococcus, the *Streptococcus epidemicus*, an organism we can follow and differentiate from other hemolytic streptococci, we came across remarkable phenomena. As in scarlet fever, the patient gets over the sore throat, becomes a carrier of the streptococcus for about two or three weeks, is apparently normal, but during the third, fourth, or fifth week develops an acute arthritis not unlike that of rheumatic fever or a glomerular nephritis, and during the time that the arthritis is active, we can demonstrate the organisms in the throat.

If one does skin tests with the organisms, one finds they give very strong reactions, and certainly there seems to be in the patient a hypersensitiveness to streptococci. We have confirmed these observations in experimental animals.

I think this hypersensitiveness demonstrated to the streptococcus should lead to more cautious use of vaccines. I believe that our promiscuous use of vaccines as

they have been used and are being used at the present time, if not conducted properly, will not desensitize patients but will possibly render them even more hypersensitive.

DR. HARKAVY.—At the outset I wish to thank Dr. Rackemann for finishing up my paper, which because of lack of time I was not permitted to do, and to re-emphasize that in drawing conclusions from skin tests made with bacterial proteins we should be very, very careful because of the many unknown factors and the complexity of the organisms with which we are dealing. The reactivity of the skin to bacterial proteins is not as simple as are skin tests to foods or pollens.

Looking for results in therapy we must also bear in mind that the removal of one allergic factor is insufficient. When bacterial infection exists associated with atopic hypersensitiveness, both are of equal importance. Both must be treated, for the allergic individual easily acquires sensitiveness to the coexisting infection.

DR. STERLING.—We do have a control group. I was not permitted to finish my paper, but I had a number of slides of a group of patients who did not have respiratory diseases at all. Patients with carcinoma or other ailments were given the same series of tests and out of the 12 patients in the group we had only one who gave a positive reaction to streptococci and one to dust. It is easily seen that only the patient who suffers from respiratory disease will respond to house dust and various bacteria.

I do not see why you should draw a line and say that if you get a pollen reaction you will treat with pollen, and if you get a house dust reaction you will desensitize with house dust, and if the same patient or another patient gives a similar reaction to bacterial suspensions, you claim that for academic reasons we are not justified in treating with bacterial suspensions. I do not believe that is right. In the patients who have both pollen and dust sensitivity, treatment with one and not the other will not give perfect results. We treat the patient with pollen, house dust and bacterial desensitization at the same time, wherever indicated, with almost a 100 per cent success.

The Pollen Allergen. J. H. BLACK, DALLAS, TEXAS. (For original article, see page 1.)

Meteorologic Aspects of the National Ragweed Problem. O. C. DURHAM, NORTH CHICAGO, ILL. (For original article, see page 58.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—Dr. Black's paper is most interesting and brings up again the old question of whether Coca and Grove were correct in stating they were able to digest all protein out of pollen antigen, and whether Dr. Black was able to do the same thing himself. Alles, working in my laboratory, disagrees with him purely on a chemical basis and proving that he was able to get protein nitrogen after carrying out the same technic and using the same material as Coca and Black did. Going a step further, he attempted with other proteolytic enzymes further to digest the nitrogen that was present, with no success. I feel as Dr. Black does that since the question of polysaccharides has arisen, it is very possible that both these solutions, one supposed to be protein-free, may have polysaccharides within them and that the so-called polysaccharide solution might contain protein. The essayist in his discussion mentions the fact that nitrogen content does not determine the activity of the protein solution, which is in accord with our own experience, and in a paper published in *The Journal of the American Medical Association* in 1924 or 1925 we brought out a similar observation with which Dr.

Coca at that time disagreed. Since then, however, his opinion has changed, he having made the admission several years later in a published article.

Mr. Durham's paper brings out the interesting fact that despite his low pollen counts there is equally as much hay fever present, which makes me think that perhaps the amount of pollen in the air does not always determine the severity nor the number of hay fever cases during that particular season. I do not believe that the amount of pollen in the air is the real factor that determines the severity or amount of hay fever each year.

DR. HARRY L. HUBER, CHICAGO.—Dr. Black spoke about the fat content of pollen. Four years ago I reported before this Association that anhydrous ether extracts of pollen show definitely positive skin reactions in a small percentage of the patients, about four or five per cent. I believe that in a small percentage of patients this is very important.

At a recent meeting at Atlantic City, Dr. Aaron Brown reported a case of pollen dermatitis due to a fat extracted from pollen.

Regarding Mr. Durham's paper about five or six years ago I reported the effects of the meterologic conditions around Chicago. We have the lake on one side of the city and have a small amount of pollen on certain days when there is a lake breeze.

Last year was a very good example of the effect of lake breezes. From August 15 to 25 we had a continuous lake breeze, a very unusual condition in Chicago. Those who had pollen disease in Chicago were going along with practically no symptoms when they stayed near enough to the lake front, and congratulated themselves that they were having a splendid hay fever year, but on August 25 the winds came from the southwest, and they all knew that something had happened. The city was flooded with pollen from the prairies southwest of the city.

In Chicago 40 per cent of the time the wind comes from the lake, and on those days the patients are always better, but many of them are not entirely free of symptoms.

DR. GEORGE L. WALDBOTT, DETROIT.—I do not see why there is so much discussion about the question whether or not a certain antigen contains protein. We know that nonprotein substances such as aspirin, quinine or any carbohydrate may produce asthma as well as anaphylaxis. It appears to me that there is a certain protein substance newly formed in the system which in its action behaves like histamin, regardless whether or not the antigen is or contains protein.

DR. WARREN T. VAUGHAN, RICHMOND.—In discussing Mr. Durham's paper and the remarks made by Dr. Piness, I want to show a composite curve of ragweed for the last four years in Richmond. The statement was made by Dr. Piness that the concentration does not necessarily determine the amount of symptoms.

In 1927 our peak of concentration was way down, around 20 per cubic yard of air, but we had almost as many cases of asthma and hay fever as we did on an average year.

The other point I might bring up is the effect of the 1930 drought. For the preceding three years, we have a graph of prevalence to compare with last year. The drought last year hit Virginia about as hard as it hit anywhere. Around the 19th or 20th of August we usually get enough pollen in the air to show on plates and enough on the nose to cause symptoms.

In 1930 there was no rain except for about a tenth of an inch around August 5, until the 28th of August, making Richmond almost 100 per cent arid throughout August until the 28th. There was no ragweed, in the air, either.

On August 28 we had 1.8 inches of rainfall in a few hours. On September 1 ragweed appeared on the plates and hay fever commenced. We had a ten-day

delay in symptoms. No one started sneezing until the first of September. We had a deficit of this amount of ragweed pollen. In the next ten days, however, there was an overproduction, and we just about made up for the deficit as compared with the average for the preceding years. Following this we had a high average pollen year.

DR. PINESS.—Did you have more hay fevers and asthmas as a result of that?

DR. VAUGHAN.—No, the same thing.

DR. J. A. CLARKE, PHILADELPHIA.—We have been studying atmospheric pollen slides for a good many years. These have been in exactly the same location. We feel absolutely certain that the amount of hay fever depends on the amount of pollen in the air. We check this in two ways, first on the results in the treated cases and second in those who have had no preseasonal treatment and who came to us for treatment in the middle of the season. The next week after high pollen counts many phylactic treatments are started.

As to which meterologic factor is the most important, we feel it is the percentage of sunshine. The absence of sunshine, the cold, damp, muggy weather we get around here does not produce pollen. We feel that the sunshine is the most important of all the factors we have to deal with.

In defense of the nitrogen content of our pollen solutions, we have been making comparative studies both in the skin and in the eye of the same patients over eight, nine, and ten years. During the early part of that period our pollen was not of as high grade as it has been lately, so that the nitrogen content, according to the method we use, would vary from 0.15 to 0.3 milligrams in the stock solution. When we diluted that down to the customary 0.001 and 0.1 mg. of nitrogen per c.c., results in the same persons are remarkably constant year after year. Those who react to the 0.001, one year, react to the same strength next year, regardless of whether the original stock solution was high or low in nitrogen.

DR. VAUGHAN.—I want to make myself clear on one point. I find, like Dr. Clarke, that with individuals whom we have had under treatment, when we get peak days, they are likely to have more symptoms. My point was that in the low pollen year we had just about as many cases of hay fever and asthma as we did in the high pollen year. I believe that there is a correlation between pollen prevalence and intensity of symptoms and that this is crudely quantitative with the higher concentrations but that there is a qualitative threshold for symptoms. Given a certain pollen concentration in the air, a majority of those who are sensitive will evince symptoms. Given twice that concentration, the number who react will not be much larger. But given still higher concentrations, the symptoms of these same people will be more pronounced. There is a threshold of pollen prevalence which sets off the trigger mechanism in the majority. Higher concentrations make the symptoms worse in these people.

DR. R. BALYEAT, OKLAHOMA CITY.—I should like to ask Mr. Durham a question concerning the 90 per cent. Did you have reference to *Ambrosia elatior?* In western New Mexico and Kansas and also western Oklahoma and western Texas there are thousands of acres of western ragweed, and it is a pretty good producer of pollen. Last year a very unusual condition existed in the Great Southwest, namely, the pigweeds and the thistle which usually pollinate profusely during the month of July produced but little pollen until the rains began about the middle of August; then they started to pollinate and pollinated throughout September. Usually they cease to pollinate about the 10th of September. This produced a situation which was an unusual one because many patients are sensitive to the pigweeds and ragweeds, or to thistle, pigweeds and ragweeds, all three. Such pa-

tients have the pigweeds and thistle to contend with during July, but when the middle of August comes, the pollination of the pigweeds and thistle is pretty well over. But last year they had all three to contend with at one time, which made the hay fever symptoms extremely severe during the first 23 days of September. We also had to contend with a south gale which lasted for 18 days, which was a very unusual one. It illustrates the fact that many factors, namely, wind velocity, rainfall, and the time during which the rain falls, play an important part in determining the importance of pollen as an etiologic factor in hay fever and asthma.

DR. I. S. KAHN, SAN ANTONIO.—In Southwest Texas we have some very peculiar things that turn up regarding the question of weather and pollen. For instance, we have very little rainfall and periods of very high winds. There is no question but that with the high winds, our number of hay fever cases increase, and also their severity; in fact, it is almost impossible to desensitize patients in our community to where they will stand the occasional days of extremely high winds without symptoms.

As Dr. Balyeat brought out, we have very little short ragweed in and around southwest Texas. Our short ragweed is *Franseria tenuifolia* and going over the Rio Grand into Mexico, we have the *Psylostachya* form and we have plenty of hay fever in and around Corpus Christi, Texas, where there is no giant ragweed at all.

We have dry seasons and wet seasons. During the dry years, sufferings from our careless weed is rather intense, and our ragweed troubles are not very severe. During wet summers our careless weed cases have little or no trouble and our ragweed cases have a great deal of trouble.

I had that same problem to meet that Dr. Balyeat has to meet where the careless weed extends into the ragweed season because careless weed in my country begins about the 15th of May and ends on or about the first of October. Ragweed with us starts the first of September and goes on into December.

The year before last I saw something I had never seen before regarding pollen. One of our heaviest pollen seasons is the cedar season which starts around the middle of December and runs to the first of February and gives us a most intense, severe hay fever. We not only have pollen to fight at that time, but we also have cold air and high winds, which gives us a very difficult situation to meet. We have some snow every three or four years, usually a light fall that does not stay on the ground very long, but the year before last we had cedar hay fever cases during the snowfall, which is the only time since I have been doing allergy work that I have seen pollen and snow in the air at the same time.

DR. BLACK.—I made no attempt in this very brief paper to abstract all the papers. I am simply trying to bring out the few salient points on each side of the matter so one might have it briefly at one's command. No attempt was made to make a complete bibliography.

Regarding Dr. Balyeat's criticisms, in our treatment of allergy I think we admit we do not know what we are doing. There is some question as to whether we are desensitizing the patients or actually building up the tolerance of these patients. Most of us believe we are not doing anything in the way of immunizing the patients, and, whether this is true anaphylaxis is open to question.

It is interesting to find out some of these things if we can. Our practical treatment of patients would be vastly improved if we could get somewhere with that.

MR. DURHAM.—The point that Dr. Vaughan brought out in regard to the pollen curve not coming up on schedule the past season and the symptoms being delayed until it did come up, agrees with all the records with which I have had anything to do in Louisville, Chicago, Knoxville, Atlanta, St. Louis, and Kansas

City. The season did not start so soon. Dr. Huber spoke about patients not having symptoms because the wind blew off the lake. That is true, but it is also true that the curve did not come up anywhere else during that time. That is exactly what happened in Indianapolis.

The sunshine factor may check out very beautifully for a season or two. A factor may correlate beautifully with the pollen curve during one season and next time not at all, but the conclusions in this paper are based on all my data with thousands of slides. Our wind curve gives better correlation than the sunshine curve.

Let me close by saying I wish to be of the utmost service in this work to any of the members of the Association at any time, in any way that I can.

A Note on the Quantitative Survey of Pollen. HARRY B. WILMER AND HERBERT M. COBE, PHILADELPHIA, PA. (For original article, see page 63.)

Distribution and Importance of the Paper Mulberry as a Cause of Hay Fever and Asthma in the United States. RAY M. BALYEAT AND HERBERT J. RINKEL, OKLAHOMA CITY, OKLA. (For original article, see page 7.)

DISCUSSION

DR. HARRY S. BERNTON, WASHINGTON.—I had the pleasure of presenting a few years ago before this Association a report on the paper mulberry as a cause of hay fever and asthma. The most striking feature was the severe clinical course of the disease in the patients who were sensitive to the pollen. In fact, the disease was most disabling.

Since my first report was published, I have had three additional cases. Dr. Balyeat has emphasized the high toxicity of the pollen. This was exemplified in one patient who developed a severe asthmatic paroxysm during the performance of a cutaneous test. Only once before in my experience have I seen a constitutional reaction result from the absorption of protein through a cutaneous scratch. In the course of treatment, the maximum dose attained was 0.05 c.c. of a dilution of 1:100,000 of pollen extract. Nevertheless, the clinical result was excellent. This patient continued at her work during her hay fever season, instead of being incapacitated with asthma. This fact brings us back again to a matter which has been discussed, namely, the standardization of pollen antigen by nitrogen determination. To my mind, such titration is of little value. After all, the patient sets the standard.

MR. O. C. DURHAM, NORTH CHICAGO.—I have not much to say about Dr. Balyeat's paper other than to compliment him on the photography. You can see this phenomenon if you gather the mulberry blossoms and put them in a glass of water. They will notify you when they are pollinating, by exploding before your eyes.

Dr. Cobe's paper did not need any apology. I am sorry he apologized for it. It is a good paper. I am interested in everything brought out in that paper.

Mr. H. A. Allard of the U. S. Department of Agriculture in Washington has made careful studies on the effect of the length of hours of sunlight on ragweed pollination and he has caused ragweeds to blossom at his own time by having them on a goecart that he can wheel into the dark when he likes, thus shortening their hours of sunshine.

Potency of the pollen is another most interesting problem. Dr. Cobe intimated that pollen is more potent some years than others because of certain conditions.

That certainly would permit of some study, but we should have some quantitative figures for that by skin tests or some other method. Dr. Cobe, you did not offer any proof, did you?

DR. COBE.—No.

MR. DURHAM.—I wonder what was accomplished by throwing the slide around into the wind. I think probably it is all right. One author turned the slides to face the wind. I think it was a mistake to keep it facing the wind in a vertical position because the wind tends to create an air cushion in front of the slide causing the pollen to glance off on both sides.

As far as the day record is concerned, I am glad somebody else attempted that. Dr. Cobe probably overlooked the record I published in the first issue of the JOURNAL OF ALLERGY. It showed a characteristic S-curve, but at nine o'clock in the evening due to a storm it ran as high as in the morning and then dropped again. Mine did not come up until seven or eight in the morning. I hope to run another. I am sure it should be made on hourly slides if possible.

My slides were exposed on top of a building and the total count for the 24 slides was within 5 per cent of the amount that was on my one slide exposed on another building the same day.

DR. WILMER.—We had the most ideal surroundings to attempt this because we were working on a sixteen-story building, as Dr. Cobe has explained, in the most advantageous location. Inasmuch as it was in a valley, the atmosphere played no part. We exposed our plates vertically because we wanted to try to get the atmospheric pressure to play some part. We really wanted to apologize because we thought that it was more or less an elementary study, but we learned a good deal from it, and I think we have all been face to face with the fact that individuals do suffer so consistently early in the morning, approximately four o'clock, or just about sunrise, and we found that on days when the atmosphere was very heavy and damp the atmosphere would tend to bear the pollen toward the surface of the earth, and the individuals complained more of asthma at that time.

We tried to prove why these individuals suffer at that time of the day, and I think there is no doubt that the pollen does settle toward the earth and they suffer more until the pollen tends to rise.

DR. GRAFTON TYLER BROWN, WASHINGTON.—I should like to ask Dr. Balyeat whether he also obtained positive reactions to skin tests with Osage orange, and white and red mulberry pollen in those patients sensitive to the pollen of the paper mulberry tree.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—I think that Dr. Balyeat's paper indicates the importance of the study of the pollinating trees, in specific communities.

In California during the last two or three years I have recognized the importance of the acacias as a cause of pollen sensitization. The acacia tree is a very brilliant flowering tree, with a brilliant yellow blossom. For some time I did not realize the importance of it as a cause of sensitization, but during the last two years I have become very definitely aware of its importance.

It is an interesting thing that there are a great many flowering species. There have been something like over 400 described, and some do not vary very much from the others. The acacia was brought in from Australia.

It is interesting that my pollen counts of the acacia in the air are comparatively very low. This emphasizes the fact in view of the occurrence of very severe symptoms from acacia that it is very toxic pollen, which corresponds with the findings of Dr. Balyeat. It produces not only hay fever and asthma but dermatitis and pollen

toxemia. I have found two patients, both adults, who have had very toxic symptoms from acacia pollen, and I have also been able to show that the toxemia has continued to a certain degree from the grass pollen as it has come into the air. This is similar to the toxemia in children due to pollen, described by Dr. Kahn some years ago.

DR. GEORGE PINESS, LOS ANGELES.—Dr. Balyeat's paper on mulberry and its method of pollination reminds me of the castor bean (*Ricinus communis*) which acts quite similarly with the exception that the male flowers when placed on glass will dry and at a certain point explode, giving a picture similar to that described by the essayist.

DR. I. S. KAHN, SAN ANTONIO.—These trees in the South, as far as hay fever is concerned, are decidedly important, and I should be delighted if anyone would pick up something else, as Dr. Balyeat has done with the mulberry tree. The trees antedate our grass pollen season, and while it is perfectly true from a laboratory point that tree pollen is specific and has no connection with grass pollen, still, from a clinical point of view there is no question, as Dr. Balyeat brought out at the meeting of the Southern Medical Association in Miami last year, that in a grass allergic patient suffering from tree hay fever who goes into the grass season with a wet nose, grass desensitization results will not be very satisfactory.

These trees vary a great deal in importance from year to year. For instance, the oak has always been a very important tree in our community. Hackberry, has not been so important. Last year the oak caused little or no trouble, and that was also true of the pecan, one of our worst offenders, but we had a good deal of trouble with sycamore.

Our Texas cedars smoke just like the mulberry that Dr. Balyeat describes. About the time my pollen plates begin to show cedar pollen, the ranch people northwest of San Antonio tell us the cedars are smoking, and we can begin to look for trouble.

One peculiar thing about this tree question that I have not seen elsewhere, and I do not know whether it occurs in other communities besides mine, I might mention. Trees are so important in a heavy pollen country where 95 per cent of our hay fever and asthma cases are pollen cases, that we test all of our patients for tree pollen sensitivity.

One very peculiar thing we have found out in our routine tests. If we test these tree cases out of the tree season, even by intradermal tests, our findings are usually negative, but if we get our tree sensitive cases back and retest them when tree pollen is in the air and hay fever has commenced, then our tests become positive.

DR. COBE.—The only thing I have to say is that I should like to make an explanation in addition to what has been said about pollen collected from a segregated area, in a field perhaps, collected, we shall say, within the first two or three days of pollination. Pollen made up into extract may give us a three-plus skin test, and two or three days afterward there will be a severe rainfall and something has changed the pollen collected from the same segregated area, whose nitrogen content has not been altered very much. It may give only a one-plus or plus-minus reaction. Apparently something has happened to the potency of the pollen in that area and that is the point I wanted to bring out here.

A Dry Pollen Ophthalmic Test in Pollen Asthma and Hay Fever Patients Negative to Cutaneous Tests. M. MURRAY PESHKIN, NEW YORK CITY. (For original article, see page 20.)

DISCUSSION

DR. HARRY L. HUBER, CHICAGO.—In patients who give a very definite history of pollen symptoms and in whom the skin test is negative with the dry pollen or the pollen extract, I think this suggestion of Dr. Peshkin's is well worth trying. I have been using it for several years and have found it very helpful. I want to ask if inhalation tests are used also.

DR. GRAFTON TYLER BROWN, WASHINGTON.—I want to corroborate everything that Dr. Peshkin has said, and to congratulate him especially on his very excellent illustrations, the originals of which are now on display in the Allergy Exhibit. I believe almost all of us agree that there is a small percentage of allergic individuals who have definite mucous membrane hypersensitiveness without a concomitant skin sensitization. Therefore, when we encounter hay fever and asthma patients with a history strongly suggestive of pollen sensitization, who give negative reactions to skin tests with the suspected pollens, it certainly seems logical to apply the pollen directly to the mucous membrane. This may be done simply and safely by means of the dry pollen ophthalmic test.

Now a few words about the technic. One of the illustrations shows the dry pollen being applied to the everted lower lid out of a vial. I think there is some objection to this method, in that too much pollen is liable to be shaken into the eye. It seems preferable to pick up a little of the dry pollen on the blunt end of a toothpick, and thus have absolute control over the amount of pollen that is to be inserted in the eye.

Dr. Peshkin stated that the illustration depicting the removal of the pollen following the completion of the test was not true, because it showed the pollen all in one place. Personally, I think that the illustration is correct, as the pollen tends to collect at the inner canthus of the eye in a stringy mass.

I concur with Dr. Peshkin in the use of dry pollen for the ophthalmic test, as innumerable comparative tests have taught me that dry pollen usually gives larger skin reactions and more definite ophthalmic reactions than the most concentrated pollen extract.

Dr. Peshkin did not mention the occurrence of nasal symptoms in the ophthalmic test. Tears incident to the reaction run down the nasolacrimal duct, thus conveying some of the pollen allergen to the nasal mucous membrane, resulting in nasal symptoms on the corresponding side.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—I shall corroborate the findings of Dr. Peshkin. I had a very interesting case just recently. I have been studying the patient, a woman for over a year. She came to me because of a marked itching of the eyes and some hay fever. I tested her and found she gave very definite reactions by the skin test to fall pollens and some cultivated flower pollens. She had symptoms in the spring and we found out by the ophthalmic test that she was also sensitive to the grass pollens which accounted for those symptoms. Her main symptoms were itching of the eyes and I observed after we made this ophthalmic test that her symptoms were improved. I thereupon began to desensitize her conjunctivae locally with dilutions of the specific pollens. I had given her prolonged thorough treatment subcutaneously with pollen extracts, without any result so far as the itching of the eyes was concerned. After the use of the local desensitization in the conjunctivae, her distressing symptoms disappeared, and I recommend this type of therapy for your consideration.

DR. I. S. KAHN, SAN ANTONIO.—This conjunctival testing method which Dr. Peshkin mentioned, devised by Miss Grothaus and myself and reported to this Association seven years ago, requires time, and is entirely too dangerous if used in sick cases, many severe, tedious relapses ensuing.

When I learned of Dr. Peshkin's dry pollen eye test, I adopted it routinely in my negative skin test cases. I can confirm the statement that it is specific, as I have often had grass tests negative in one eye and ragweeds or careless weeds positive in the other, and vice versa. Also it is quickly and easily done and the pollen easily removed when reaction starts and a few drops of adrenalin in the eye quickly remove reaction discomfort. It will produce hay fever and asthma. Also it has the disadvantage of scattering antigenic material where there is a possibility of annoying very sensitive cases.

In the very ill patients it gives but little information and it also gives relapses. In the low degree sensitivity cases I should say that it has revealed the etiologic diagnosis in about 10 to 12 per cent.

Something like 35 per cent of the pollen hay fever and asthma cases of my community are nonskin reactors. This figure sounds astounding, but when one considers that there are only two to three weeks in the entire year in which South and Southwest Texas does not have high antigenic pollen in the air, with frequent high winds and only two or three months of the year when mild weather does not encourage outdoor sleeping and living, plus one of the worst seasons in midwinter, it can be realized at once that such a community might show some rather extraordinary results.

Lieutenant-Colonel S. W. French, of our local army hospital, who has previously worked with Drs. Cooke and Coca, for some three years, has been stationed for the past four years in San Antonio, and he confirms these findings. In addition, San Antonio is a health resort drawing advanced, sick, chronic perennial asthmatics, and many of these, of course, are nonskin reactors.

DR. WARREN T. VAUGHAN, RICHMOND.—I shall enter the lists with Dr. Peshkin against Dr. Brown. I usually find the pollen strung along in mucus, and you can dip in with cotton on a toothpick and take the whole thing out without any trouble whatsoever.

He did not describe the 6-plus reaction, which I have seen in a woman who was sensitive to giant and short ragweed. Her seasonal occurrence was right for ragweed. Skin tests were negative. I put the dry pollen in the conjunctival sac and in addition to the lacrimation, she had an edema of the entire lid both upper and lower. With local cold applications and adrenalin, it was gone in an hour and a half or two hours, with no after effects.

We have a lot of wire grass sensitization down our way, and I have felt, purely from the superficial resemblance, that wire grass and Bermuda grass and crab grass were probably quite closely related, but I have recently seen a man who was negative to all of these by scratch, distinctly positive to wire grass by ophthalmic reaction, and negative to Bermuda and crab grass by eye test. I did passive transfers and found that wire grass only reacted, and apparently from the information available there does not seem to be quite so close a relationship as I felt that there was.

I should like to ask Dr. Peshkin two questions. One is about a man who has hay fever in the grass season who is entirely negative by skin tests. I saw him just last week. I tested him about every two hours with different dry pollens. He had the ophthalmic reaction applied in alternating eyes. You can run several tests in one day provided you do not get a positive reaction. When we struck timothy, he had practically a negative reaction, but developed quite a bit of sneezing and rhinorrhea afterward, and I should like to know the interpretation of that.

Has Dr. Peshkin made any attempt to gauge the degree of desensitization with the ophthalmic tests as a control?

Of course we know that the disappearance of a positive skin reaction does not necessarily mean that the patient is not going to have hay fever or vice versa,

but this year with those cases that we have been carrying along with perennial desensitization. I have recently applied ophthalmic reactions with the hope that if that was negative, we should have some advance information. They have all been positive to the eye test and yet have been able to go through the season without symptoms. Of course the concentration in the eye is much higher than one would find in normal exposure during the season.

DR. PESHKIN.—I am sorry I was unable to read the entire paper in the time allotted me. In regard to Dr. Huber's question with reference to the nasal test with dry pollen, I have not employed this test and do not expect to, for many reasons. The nasal mucous membrane of most patients with pollen allergy is more sensitive than in those without allergic disease. Traumatic reactions of the nasal membranes are therefore expected to occur frequently in allergic patients, and the classification and differentiation from positive reactions no doubt offer many difficulties. The daily spraying of dry pollen in an allergist's office is certainly not going to make such an environment the most ideal for hay fever and asthma patients. However, this method of testing may be indicated in a small selected group of cases. For patients refractory to pollen by the cutaneous test, the dry pollen eye test is obviously the test of choice.

The dry pollen eye test is best controlled with pine pollen because a positive reaction with pine pollen has not yet been obtained. For this reason it also serves as a valuable control in the testing of patients exhibiting "ophthalmographia."

The majority of patients with vernal catarrh show negative reactions to pollen with the cutaneous test. The dry pollen eye test is positive in a small percentage of these patients. However, on the basis of seasonal recurrence among other factors, I have since 1922 treated with pollen all patients with vernal catarrh and have obtained satisfactory results.

In answer to Dr. Vaughan's question about the occurrence of sneezing on the same side of a negative dry pollen eye test, I wish to state that such a reaction occurs only occasionally. What the significance of this reaction has been I am unable to state at this time because the number of cases encountered is too small to permit one to draw definite conclusions.

Dr. Vaughan's last question in reference to the use of the dry pollen eye test during the course of specific desensitization treatment as a means of controlling the dosage of pollen in patients negative to the cutaneous tests. Experience has demonstrated that as a rule these patients require large doses of pollen for protection. As a matter of fact many patients in whom specific treatment has been successful do not at any time show a local reaction at the site of the injection. As a result of such treatment a positive dry pollen eye reaction is seldom abolished. The use of such tests as a means of controlling treatment would serve no purpose. The guide to optimum protection doses is entirely a clinical one, and the allergist should keep in mind the fact that these patients tolerate and require high doses of pollen for protection from the symptoms of pollen allergy.

Department of Reviews and Abstracts

Selected Abstracts

Investigations Into the Chemical Nature of Allergens. Loeb, L. F.: Biochem. Ztschr. **220**: 432, 1930.

Previous observations have led the author to believe that the working principle of pollen allergens is a protein, or bound to a protein, or active only in combination with a protein. This view is contrary to that held by every other worker, including Coca and his coworkers.

Experiments are carefully carried out upon a large number of guinea pigs. The pollen extract to which the animals were sensitized, was fractionated, and a very delicate and exact chemical analysis made upon the various fractions. The author states that Coca considered his extract to be protein-free when the nitrogen content corresponded with, or approximately corresponded with, the nitrogen content of the control solution (extraction fluid and trypsin). The author gives data to show that therein lies an error; that the analysis is not sufficiently delicate to demonstrate a quantity of protein remaining, a small amount but still sufficient to precipitate a reaction.

Further experiments confirm the author in his belief that the working principle of pollen allergen is a protein, or bound to a protein or active only in combination with a protein.

A Consideration of the Air Passages. Hofbauer, L.: München. med. Wchnschr. **78**: 232, 1931.

The histologic structure of the mucous membrane of the air passages with its resultant susceptibility to slight temperature changes is described in great detail. The effect which is a disturbance in the delicate mechanism governing the functioning of the air passages, such as is found in asthmatic conditions, and measures for their alleviation are dwelt upon at length.

Report on Asthma Research at Stobhill Hospital, Glasgow. Adam, J.: Glasgow M. J. **116**: 81, 1931.

The report covers an investigation of eighteen months, relating mainly to adults.

Eosinophilia was found to characterize most cases of asthma.

Urea raised the eosinophile count in one to two hours after ingestion. Fifteen grams was the dose given in 23 cases. In 18, there was a definite increase of eosinophiles both in percentage and actual number. The five cases showing no increase, had no asthma in the hospital, and the eosinophile count was about normal. Adrenalin, when the eosinophile count was normal, produced little change; but, where there was an eosinophilia, it produced a prompt fall in the count with a concomitant slight rise in the alkali reserve. Atropin ($\frac{1}{100}$ gr. hypodermically) had an action similar to that of adrenalin. Cold douche, following a warm bath, had the effect of diminishing the eosinophile count and bringing relief from asthmatic attack. Such action is explained by the effect of cold after heat in stimulating adrenals and thyroid and in causing prolonged adrenalin flow. Pyrexia caused fall of eosinophile count, due in part, it is suggested, to the stimulation of the adrenals. Menstruation usually is accompanied at the onset by a rise in the eosinophile count and an increase in the asthmatic symptoms. Ingestion of liver was found usually to aggravate asthmatic symptoms. It is known that the ingestion of liver raises the eosinophile count. Detoxication, by diet, water-drinking, exercise, laxatives, etc., reduced the eosinophile count and raised the alkali reserve.

The view previously held by the author that in asthma there is an acidotic tendency was upheld by the findings of the decline in alkali reserve at the attack and therefore at the time of increased CO_2 tension in the lungs, its rise with detoxication and vanishing of bronchospasm, an increase of ammonia-combined acid in the urine at end of an attack, and a chloride shift to the corpuscles. It is admitted that there may be in children a swift change to alkalosis, but it is contended that this is to meet the acidosis. Tables and case reports are given.

Allergic Reactions in Polio-Convalescent Children After Intracutaneous Injection of Heat-Inactivated Poliomyelitis Virus. Jungeblut, C. W.: Proc. Soc. Exper. Biol. Med. **28**: 1072, 1931.

The work is a continuation of previously published experiments on the accelerated febrile response of convalescent monkeys to reinoculation with poliomyelitis virus. In this report 27 children and youths with a definite previous history of poliomyelitis were selected for experiment. They were inoculated intracutaneously on one arm with 0.2 c.c. of a Berkefeld filtrate of a 5 per cent monkey virus emulsion, inactivated by heating for one hour at 65° C. Into the other arm was injected intracutaneously a similar amount of filtered and inactivated 5 per cent emulsion of normal monkey cord for control. All of the 27 subjects reacted to the killed virus in a typical allergic manner—urticaria, erythema, etc. The control emulsion elicited no reaction.

The same experiments run upon normal individuals indicated a preponderance of positive reactions in adults over those obtained in younger children. The conclusion is drawn that in all probability the majority of older children and adults are protected against poliomyelitis by past latent infection which has induced the production of antibodies against the virus.

Psoriasis and Asthma. Brock J.: München. med. Wchnschr. **77**: 2225, 1930.

The question of a relationship between psoriasis and asthma which has been brought up for discussion several times is commented upon. The author contends that a fundamental diathesis underlies both conditions. No experimental proof or extensive case reports are given, and conclusions are reached by deduction. This is based upon the fact that asthma, gout and psoriasis are often associated, a condition of which the author speaks as "visceral gout." Moreover, treatment for gout has been found to improve both asthma and psoriasis.

Skin Reactions of Patients and Normal Individuals to Protein Extracts of Streptococci. Derick, C. L., and Fulton, M. N.: J. Clin. Investigation **10**: 121, 1931.

The work was undertaken with the object in view of ascertaining the type and degree of response to an intradermal injection of streptococcus antigens in a large group of general hospital patients. Six hundred and seventy individuals were tested, of varying ages and suffering from a variety of diseases. Fifty-eight supposedly normal adults, in addition, were tested for controls.

The nucleoproteins were extracted and precipitated repeatedly until their nitrogen content was constant. All solutions were cultured aerobically and anaerobically on liquid and solid media to insure sterility. The nucleoproteins used were: those from hemolytic streptococcus, green streptococcus and ordinary baker's yeast (for control). Injections were made into and not beneath the skin. The amounts used were, for the most part, 0.001 mg. of hemolytic streptococcus nucleoprotein (dissolved in normal salt solution) and 0.003 mg. of each of the others.

Measurements of reactions were made at the end of twenty-four hours and usually every twenty-four hours thereafter for at least three days.

Results showed that the hemolytic streptococcus nucleoprotein almost uniformly induced stronger reactions than did the green streptococcus nucleoprotein. In subjects over fifteen years, age apparently played no part in the condition of sensitiveness or lack of sensitiveness to the antigens. In children under fifteen years of age, the proportion

of positive to negative reactions increased with increase in age. This was shown particularly in the group suffering from rheumatic fever.

It was found that positive reactions to the nucleoproteins were elicited in a great variety of diseases. The test was therefore considered to be of no specific diagnostic value.

The Influence of Surgical Intervention on Asthmatic Crises. Vallery-Radot, P., Blamoutier, P., and Claude, F.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**: 416, 1931.

A résumé is given of eleven cases in which asthmatic crises, previously severe and of great frequency, were interrupted by surgical intervention. The interval, following operation, during which the patient remained free from attack varied greatly—fifteen days, two months, six months, even longer. This phenomenon has been noted before, and various theories have been offered in explanation. For example, it has been suggested that the inhibitory action is due to the general anesthesia. This may be admitted to explain some cases, but in the opinion of the present authors leaves unexplained those cases in which only a local anesthetic was used. No explanation so far advanced has been found to cover all of the circumstances.

Six cases are presented in which surgical intervention apparently initiated the asthmatic crises or replaced a spasmodic coryza by asthma.

In conclusion, it is stated that it is conceivable that surgical intervention could modify the state of the vegetative nervous system and consequently initiate or stop the crises. Whatever the pathogenesis, the clinical fact remains that surgery can produce either effect, according to circumstances.

Observation on Sensitivity to Dust Fungi in Patients With Asthma. Flood, C. A.: J. A. M. A. **96**: 2094, 1931.

Fifty-five patients, 18 of whom gave positive skin reactions to dust but the majority of whom gave no indication as to the offending allergen, were tested intradermally with eight or nine extracts of fungi. Eight positive reactions were elicited. Attempts were made to incite asthmatic attacks by spraying the throats of patients who gave pronounced positive skin reactions, with filtrates of the fungi. In only one case was this successful. A detailed report of that case is given.

Bronchial Asthma and the Vegetative Nervous System. Peters, M., and Dennig, H.: Deutsch. Arch. f. klin. Med. **169**: 236, 1930.

Observations were made upon 13 patients suffering from typical bronchial asthma in varying degrees of intensity, and corresponding observations were made upon normal subjects. Results showed that

in respect to the various vegetative stigmata—blushing, paling, lachrymation, vomiting, sweating, etc.—while there were individual variations, still when an average was taken, there was no appreciable difference in these reactions in daily life, between the asthmatic and the normal individual. Nor in the pulse rate or the reflexes that mark frequency and rhythm changes in the heartbeat was any appreciable difference noted. Tables are given.

Pharmacologically, some differences were found. In general, asthmatics showed a low sensitiveness toward adrenalin, a less marked and not so general hypersensitiveness toward pilocarpine and a still slighter hypersensitiveness toward atropine. Tables are given.

Allergic and Infectious Conditions of Upper Respiratory Tract in Children. Cohen, M. B., and Rudolph, J. A.: J. A. M. A. **97**: 980, 1931.

Three classifications of conditions of the upper respiratory tract in children are made: (1) allergic, (2) infectious, (3) allergic + infectious. The symptoms in all three types are somewhat similar, so that a careful consideration of the possibility of allergy is urged. It is pointed out that the family history is of great importance. The allergic child, moreover, usually exhibits other manifestations of allergy.

Attacks, due to allergy in the upper respiratory tract, are usually recurrent, do not completely clear up, are not contagious and are not related to exposure to other cases. The visible mucous membranes are pale, glistening and edematous. Discharge usually shows an eosinophilia. The authors consider it a safe rule to regard a smear of nasal or bronchial secretion showing 10 per cent or more of eosinophiles, as diagnostic of allergy. The absence of eosinophiles does not necessarily preclude the possibility of allergy. The authors warn against two common fallacies: (a) diagnosis of sinus disease from cloudiness on the roentgenogram; (b) overdependence upon skin tests.

The article is illustrated with photographs of a section of an allergic skin wheal, of a bronchus showing edema and infiltration of the submucosa by eosinophiles, of a normal bronchus, and of an infected nasal mucous membrane showing the infiltration of the submucosa by mononuclear and occasional polymorphonuclear leucocytes with no eosinophila or edema.

Hypersensitiveness to Wool Fat. Sulzberger, M. B., and Morse, J. L.: J. A. M. A. **96**: 2099, 1931.

Two case reports are presented in some detail. The patients both presented an eczematous, dry and fissured, scaly eruption on the hands, wrists, and forearms. Otherwise, they were both healthy men. The skin affection had appeared, intermittently for six years. During

treatment, it was observed that the condition became worse upon the application of ointments. Skin tests were then made with dilutions of the ingredients used in the ointments. Wool fat applied as a patch test gave a distinctly positive reaction.

The other ingredients produced negative reactions.

Both patients improved greatly when contact with wool was avoided and when ointments without wool fat were substituted for the original medicaments. Both patients were employed in occupations involving the handling of woolen materials.

In view of the almost general use of wool fat as a base for ointments, it is suggested that some of the not inconsiderable number of patients with eczema who do not react well to treatment with ointments may be hypersensitive to wool fat.

A Fatal Case of Quincke's Disease With Painful Abdominal Crises Accompanied by Vascular Spasms. Vallery-Radot, P., and Blamoutier, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**: 549, 1931.

A case is reported in great detail of a patient suffering from Quincke's disease for a period of twenty-two years. There was no family history of urticaria or angioneurotic edema, nor had the patient through childhood or adolescence shown any symptoms of urticaria, headache, asthma, etc. In 1904 at the age of thirty-one years, he was seized one day with no apparent cause, with acute gastric pain and nausea which lasted for several hours. By the following day, the attack had subsided. From that time on, for something over twenty years, a week rarely passed without an attack. These attacks were characterized by extreme fatigue, pain and nausea, the patient at times being unable to retain even a teaspoon of water. Frequently, but in no constant manner, edema was present, the localization varying widely. Upon one occasion there was an edema of the glottis so severe that tracheotomy was contemplated. From that time on he always carried with him a laryngeal tube. The edema never appeared unaccompanied by gastrointestinal crises. Vascular irregularities developed in later years. In 1924, the patient was hospitalized for careful observation. The abdominal symptoms and the vascular signs dominated the clinical picture. The edema, although characteristic, constituted manifestations of the second order.

The blood count showed an instability of white corpuscles; during an attack the P_H and the alkaline reserve were raised; the basal metabolism fell within normal limits; all skin tests gave negative results.

None of the many therapeutic measures met with success. Strict diets were tried with no results. The patient died suddenly, probably of an acute edema of the glottis.

Eczema. Becker, S. W.: J. A. M. A. **97**: 983, 1931.

The author defines eczema as "dermatitis, characterized by vesiculation in a patient who is hypersensitive to the irritative agent." It is this element of hypersensitiveness that distinguishes eczema from dermatitis venenata. There is no clinical or microscopic difference. Diagnosis is often rendered difficult by the fact that the original picture of eczema is often confused because the patient in attempting relief has used irritating applications that produce dermatitis venenata.

In the opinion of the authors, desensitization therapy in cases of eczema is unsatisfactory. The chief measures of relief advocated are local. In the vesicular stage, the wet dressing of potassium permanganate in the strength of one grain to a pint of water is suggested. After the acute symptoms have subsided, a sulphonated bitumen zinc paste should be applied. Warning is given against the use of irritating salves and ointments. Case reports are given.

Book Reviews

Until the year past, the publication of books that dealt solely with phases of allergy was very occasional. In the last twelve months, however, no less than ten such books, including new editions, have appeared. Some of them are considered important contributions to the literature. Hereafter, book reviews will appear from time to time in the JOURNAL OF ALLERGY, beginning in the present issue which initiates Volume III. As this Journal is published bimonthly, it seems feasible to review only those books which have been published within the past few months, in order to keep the reviews current.

The Editor.

ASTHMA AND HAY FEVER IN THEORY AND PRACTICE. Arthur F. Coca, M.D., Matthew Walzer, M.D., and August A. Thommen, M.D. Cloth. Pp. 851, illustrated. Charles C. Thomas, Springfield.

This book completely fulfills its title, inasmuch as its pages contain an exhaustive exposition of the theory and practice of asthma and hay fever. Although it is truly encyclopedic in the wealth of information it contains, the arrangement of its subject matter is unusually successful in permitting one to obtain readily the data at hand. The book, therefore, serves admirably as a manual for both the student and the practitioner of allergy.

Each of the authors has written one of the three parts into which the book is divided. Part one, by Coca, treats of hypersensitiveness. Various phases of this subject, such as anaphylaxis, atopy, serum disease, etc., are considered separately. The relationship of these phenomena to each other has been a matter of dispute among immunologists. In this book Coca restates his theory of a distinct separation between anaphylaxis and atopy. He makes a strong case in support of his contention; and in doing so he elaborates upon opposing points of view, so that much of the literature on the subject becomes revealed. There is much practical information in this part of the book, particularly a chapter giving the details of the preparations of extracts and solutions for use in testing and treating in human hypersensitiveness.

Part two by Walzer deals with asthma. It is undoubtedly the most complete single exposition of the subject in the literature. There are many disputed questions concerning various phases of asthma. On most of these, the author presents a painstaking analysis of the evidence at hand which he then summarizes. On rare occasions he loses

this good judgment and proceeds to build up a case to fit his own convictions. Here he is not so successful. One such instance is the manner in which he opposes the generally accepted viewpoint that bronchospasm is a primary lesion in bronchial asthma. These, however, do not detract from the usefulness of his contribution. The treatment of asthma is dealt with fully. Of particular practical importance are the chapters on methods of testing and on atopens. These are treated in great detail and should be most useful to those who are interested in skin testing.

Part three by Thommen is devoted to hay fever in which there are fewer controversial matters to be considered than in the first two parts of the book. This permits more statements of accepted facts. Fully half of the section is devoted to the botanical aspect of the subject. This is treated in detail and is profusely illustrated. The remainder deals with the clinical features of hay fever, particularly the treatment of the condition which is fully elaborated. An extensive bibliography is appended to each of the sections.

As a book of reference or as a clinical guide, this book should be indispensable.

ALLERGY AND APPLIED IMMUNOLOGY. A HANDBOOK FOR PHYSICIAN AND PATIENT, ON ASTHMA, HAY FEVER, URTICARIA, ECZEMA, MIGRAINE AND KINDRED MANIFESTATIONS OF ALLERGY. Warren T. Vaughan, M.D. Cloth. Pp. 359, illustrated. The C. V. Mosby Company, St. Louis.

This book, intended as a guide for patient and physician, is very useful. It is written in an informal style and is easy to read. It covers an amazing amount of ground and accomplishes this by subdividing its chapters into brief sections. Each of these sections is headed by titles which are followed by short discussions in simple terms of the subject matter.

It is often a difficult thing for one well versed in a complex subject to make a simple exposition of it. In this book, at times the author reveals his wide knowledge of his subject, and forgets his audience. This, however, in no way detracts from the practical value of the book. Those who practice allergy will do well to distribute this book among their patients, for it will tell in simple terms the many things the patients should know. The book will also serve physicians unfamiliar with allergy who wish to get their first insight into it. Consequently, as a handbook for physician and patient it well serves its purpose.

Correspondence

Iowa City, Ia.,
Oct. 5, 1931.

Editor, JOURNAL OF ALLERGY,
St. Louis, Mo.

Dear Sir:

The perennial treatment of hay fever is now meeting with great favor. Undoubtedly it will become the standard method. The history of its development is of interest. So far as I know the first advocacy of this treatment was presented by me in a paper read before the Iowa State Medical Meeting on May 12, 1925. In discussing treatment for hay fever I said, "I am treating my cases the year around, giving a small dose of potent solution twice monthly." This was published in the *Journal of the Iowa State Medical Society* the following year, June, 1926.

At the third annual meeting of the Association for the Study of Allergy at Dallas, Texas, on April 20, 1926, I gave a report of the perennial treatment of twelve children and twenty-nine adults, all of whom had had at least three years' treatment. The treatment was started regardless of the time of year, beginning with the solution which the patient would tolerate and gradually increasing the strength until the patient was taking the maximum dose. At this stage the treatment was given biweekly or monthly, but much more frequently during the time of building up the tolerance—usually every third day. Also the frequency was increased a month before the beginning of and continued throughout the season. During the season the quantity was decreased according to the individual's susceptibility.

This paper was not published. The Association had no journal at that time and the interest produced by the paper did not seem to make its publication urgent. It will appear in full in the November issue of the *Medical Women's Journal.*

Yours very sincerely,

ZELLA WHITE STEWART, M.D.